Advancing orthostatic hypotension diagnostics

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Advancing orthostatic hypotension diagnostics

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Advancing orthostatic hypotension diagnostics

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Chapter 1

General introduction

Orthostatic hypotension

As the average age rises globally, disorders of blood pressure (BP) regulation become more prevalent.[1,2]

BP dysregulation often becomes manifest when challenged by postural change such as standing up from supine position. Upon standing up, gravity pulls approximately 500mL of blood into the lower legs, decreasing venous return, cardiac preload and therewith BP, after which several compensation systems come into play to attenuate this BP drop and the resulting reduction in cerebral blood flow.[3–5] The baroreflex senses the BP drop by stretch receptors in the aortic arch and carotid arteries, and increases heart rate and peripheral artery resistance by narrowing peripheral artery diameter (vasoconstriction) through a neural control loop, thereby increasing BP.[5–7] Cerebral autoregulation aims to compensate for fluctuations of cerebral blood flow and oxygenation during BP drops by dilation of brain arterioles.[8] Apart from these automatic mechanisms, voluntary actions such as activating the calf muscles may attenuate the BP drop after standing up.[9]

Orthostatic hypotension (OH) according to the consensus definition occurs when BP drop after standing up exceeds the threshold (20 mmHg for systolic BP (SBP) and 10 mmHg for diastolic BP (DBP)) within 3 minutes after standing up and is sustained. OH is prevalent in geriatric outpatients (22-56%), sometimes accompanied by orthostatic intolerance (dizziness, light-headedness and blurry vision)[10,11] and associated with poor clinical outcome (cardiovascular diseases, impaired cognitive performance and mortality).[12–15] However, studies on the association between OH and physical functioning and falls are contradictory and need resolution.[5,16,17]

The consensus OH definition is particularly developed for sphygmomanometer BP measurements, not taking BP changes within one minute after standing up into account. Continuous beat-to-beat BP measurements can alternatively be used,[5,12] enabling the assessment of BP changes within one minute after standing up. These BP changes may be clinically relevant by reflecting the effectiveness of the aforementioned compensation systems,[5–8] and hence be incorporated in an enhanced OH definition. The currently available complementary OH definition addressing BP changes within 1 minute after standing up is initial OH, defined as an SBP/DBP drop magnitude of at least 40/20 mmHg within 15 seconds after standing up.[5] However, the clinical relevance of initial OH is insufficiently clear and its prevalence is higher in younger adults compared to older adults,[18] suggesting that initial OH is not a fingerprint of pathological orthostatic BP regulation. Orthostatic BP drop rate (i.e., the steepness of orthostatic BP drop) is a parameter potentially better reflecting the challenge to BP regulation systems and its clinical value therefore needs to be addressed.

The consensus OH definition does not fully clarify the distinction between OH and non-OH as it includes the condition that the BP drop should be sustained, which

is an absence of BP recovery, but lacks further specifciation.[12] As a result, different definitions of BP recovery were used in large population studies.[15,19] It needs to be assessed whether orthostatic BP recovery is clinically relevant and how to further specify its definition.

In summary, the current OH definition needs clarification on its association with physical functioning and falls, and its potential enhancement by incorporation of parameters expressing BP drop rate and BP recovery derived from continuous BP measurements.

Current gap in orthostatic hypotension diagnostics

Prerequisites for diagnostics

The association between OH and poor clinical outcome has been demonstrated in population studies.[12–15] However, the relationship between OH and clinical outcome in the individual patient still needs to be understood, requiring the measurement of relevant aspects of individual BP regulation such as compensation by the baroreflex, peripheral vasoconstriction and cerebral autoregulation.[6–8,20] Differences within individuals may arise from circadian rhythm, meals, fluid and salt intake, exercise and fatigue and should ideally also be taken into account.[4,21] The ideal OH assessment should therefore measure the aforementioned compensation systems, be long-term (i.e., 24 hours) in the home situation and enable identification of individual patients with high risk for poor clinical outcome.

Current state of the art diagnostics

In most geriatric outpatient clinics, intermittent BP measurement using a sphygmomanometer is the only device available for diagnosing OH. This measurement has three disadvantages: 1) Due to the low time resolution a large part of the orthostatic BP curve is not recorded, particularly the part within 1 minute after standing up, in which the largest BP drop typically occurs. Diagnosis of initial OH is hence impossible using this method. 2) Intermittent BP measurement does not fully reflect the individual's physiological compensation, impeding elucidation of the relationship between OH and clinical outcome on the individual level. 3) This onetime clinical measurement does not take variation within individuals into account as it does not allow for long-term measurements.

Continuous BP monitors available in some geriatric outpatient clinics overcome the first disadvantage by using the volume clamp method, implying that the pressure of an inflatable finger cuff is continuously adapted to keep finger arterial transmural pressure at zero, enabling the derivation of blood pressure.[22] These measurements allow for the assessment of both the magnitude and rate of initial orthostatic blood pressure drop as well as BP recovery as a function of time. However, it is still unknown whether these parameters have additional clinical value compared to the currently used OH definition and whether they should be incorporated in the OH diagnosis.

Continuous blood pressure monitors based on the volume clamp method can estimate baroreflex sensitivity, but not cerebral autoregulation or vasoconstriction, implying that disadvantage 2 does apply for these types of monitors. Furthermore, as these devices continually adapt finger cuff pressure, they are typically inconvenient for patients to wear for longer periods of time and hence retain disadvantage 3.

Transcranial Doppler (TCD) is an ultrasound technique that can be applied at the temporal window to measure blood flow velocity in the medial cerebral artery based on the Doppler principle.[23] When combined with a continuous blood pressure monitor, TCD can be used to estimate cerebral autoregulation.[24] However, as this technique requires continuous presence of a skilled investigator, this technique is most often used in a research setting and disadvantage 2 does still apply.

Non-invasive assessment of baroreflex sensitivity, peripheral vasoconstriction and cerebral oxygenation and autoregulation using PPG, ECG and NIRS

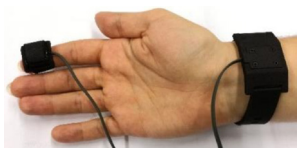
The assessment of baroreflex sensitivity requires measurement of changes in heart rate and blood pressure and may be performed using electrocardiography (ECG) and photoplethysmography (PPG). ECG enables heart rate monitoring by detecting the time between subsequent R-peaks, while BP may be estimated non-invasively using photoplethysmography (PPG), which measures the absorption and reflection of light.[25–27] When applied to superficial arteries such as the radial artery in the wrist and the digital artery in a finger, PPG can detect changes in artery diameter due to BP pulses, potentially enabling BP estimation.[25–27]

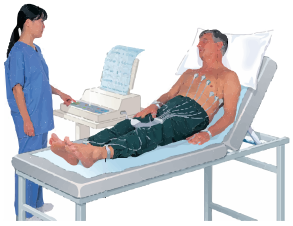
Peripheral vasoconstriction may be reflected by pulse transit time (PTT), which can be measured using PPG and ECG. PTT is defined as the time between electrical activation of the ventricles (ECG R-peak) and the arrival of the BP

Intermittent BP measurement


Continuous (beat-to-beat) BP measurement


Transcranial doppler (TCD) measurement


Photoplethysmography (PPG)


Electrocardiography (ECG)


Near-infrared spectroscopy (NIRS)

Figure 1.1. Demonstration of cardiovascular measurements. BP: blood pressure.

pulse wave at the PPG measurement site and was reported to be sensitive to pharmacological vasoconstriction and vasodilation due to the induced changes in arterial complicance.[28–31]

Orthostatic changes in cerebral oxygenation may be measured using near-infrared spectroscopy (NIRS). NIRS can be applied to the forehead scalp and measures the reflection and absorption of light in brain tissue, from which changes in oxygenated and deoxygenated hemoglobin concentrations in the frontal brain lobe can be derived based on the modified Lambert Beer law.[32] As changes of cerebral hemoglobin concentration to a large extent depend on the cerebral blood flow, NIRS may reflect changes in cerebral blood flow, potentially enabling its use as a monitor of cerebral autoregulation if combined with a continuous BP monitor.[33,34] NIRS needs validation as a suitable technique to assess cerebral autoregulation.

In summary, the combination of PPG, ECG and NIRS (Figure 1.1) may overcome the aforementioned disadvantages as it potentially provides continuous beat-to-beat information (advantage 1) about both BP changes and physiological compensation (advantage 2) in a non-obtrusive way suitable for further development for application in the home setting (advantage 3). Parameters expressing baroreflex sensitivity, peripheral vasoconstriction, cerebral oxygenation and autoregulation derived from combined PPG, ECG and NIRS measurements need to be assessed with regard to their sensitivity (i.e., the capacity to record physiological changes in response to postural change), test-retest reliability (i.e., the property to measure similar values during similar postural changes), and validity (i.e., the extent to which the parameter reflects the underlying physiology) during postural changes.

Clinical outcome

OH measurements only have clinical value if they are associated with clinical outcome, i.e., clinical measures expressing the physical or cognitive abilities or vulnerabilities of patients. In this thesis, the clinical relevance of parameters expressing BP drop magnitude, BP drop rate and BP recovery derived from intermittent and continuous BP measurements is assessed based on their association with physical functioning, physical performance, cognitive performance, frailty and falls.

Physical functioning denotes the ability to perform daily life activities and its measurement does not require standardized procedures in a clinical settings or a lab. Physical functioning measures used in this thesis are activities of daily living scales (ADL), i.e., the extent to which an individual is able to independently maintain personal hygiene, bathe, dress, eat and transfer to a different place;[35] mobility, i.e., the ability to walk to a desired place without the help of a third person or walking aids; and physical activity.

Physical performance signifies the performance on a predefined and standardized test, which most often requires a clinical or lab setting, or a trained

observer. Physical performance measures used in this thesis are the chair stand test (i.e., the time it takes a person to stand up from sitting position and sit down again five times as quickly as possible),[36] the timed up and go test (i.e., the time it takes a person to stand up from a chair, walk 3 meter, turn, walk back and sit down again),[37] hand grip strength (i.e., the maximum measured hand grip strength after three attempts with both hands),[38] walking speed (i.e., average self-preferred walking speed on a 4-meter walking trajectory)[36] and balance performance (i.e., the ability to maintain side by side, semi tandem and tandem stance for at least 10 seconds).[36]

Cognitive performance is measured using the Mini Mental state Examination (MMSE) in this thesis. The MMSE assesses orientation to time and place, attention, calculation, recall, language, repetition and complex commands.[39]

Frailty scales aim to combine a patient's vulnerabilities in several domains into one composite score. The frailty scales used in this thesis are the Fried scale assessing unintentional weight loss, exhaustion, physical inactivity, gait speed and hand grip strength;[40] and the Rockwood scale, assessing mobility, incontinence, cognitive function and activities of daily living.[41]

Falls may be assessed subjectively (e.g. by asking the patient) or objectively (e.g. using instrumented measures or objective observers), and prospectively or retrospectively. In this thesis, subjective and retrospective reports of falls are used as these were most widely available.

The different clinical outcome measures used in this thesis are complementary as they assess what patients usually do (physical functioning) and what patients are able to do when challenged (physical and cognitive performance) as well as their vulnerability for diseases (frailty) and falls.

Thesis aims

This thesis addresses three aims. The first aim is to further determine the clinical value of the currently used consensus OH definition by pooling the existing evidence regarding the association between OH and physical functioning and falls. The second aim is to assess the clinical value of assessing BP drop rate and BP recovery derived from continuous BP measurements, which may reflect the challenge posed to compensation systems and brain exposure to low perfusion pressures, respectively. The third aim is to assess the sensitivity, test-retest reliability and validity of parameters expressing baroreflex sensitivity, peripheral vasoconstriction, cerebral oxygenation and autoregulation derived from combined PPG, ECG and NIRS measurements.

Thesis outline

An overview of the contents of this thesis is given in Figure 1.2, which shows the performed measurements, the derived parameters and the thesis chapter in which each parameter is assessed.

Chapters 2 and 3 (part 1) address the association between OH and physical functioning **(chapter 2)** and falls **(chapter 3)** using systematic review and meta-analysis in older adults, geriatric outpatients, hospitalized patients and nursing home residents.

Chapters 4 – 6 (part 2) address the association between parameters derived from continuous orthostatic BP measurements and clinical outcome. **Chapter 4 and 5** address the clinical value of orthostatic BP drop rate (i.e. speed) compared to BP drop magnitude and **chapter 6** addresses the clinical value of BP recovery.

Chapters 7 – 11 (part 3) address baroreflex sensitivity, peripheral vasoconstriction and cerebral oxygenation and autoregulation derived from combined PPG, ECG and NIRS measurements. In **chapter 7**, the sensitivity of cerebral oxygenation changes measured with NIRS and the dependency of this sensitivity on the type and speed of postural change is assessed in young adults. **Chapter 8** describes the test-retest reliability and validity of the baroreflex sensitivity and cerebral autoregulation parameters derived from PPG, ECG and NIRS measurements in young adults. **Chapter 9** addresses the sensitivity, test-retest reliability and validity of pulse transit time in younger and older adults. **Chapter 10** describes age-related differences in baroreflex sensitivity and cerebral oxygenation changes during standing up in younger and older adults as an indication of validity. **Chapter 11** addresses the validity of NIRS-derived cerebral autoregulation estimates using TCD as a gold standard.

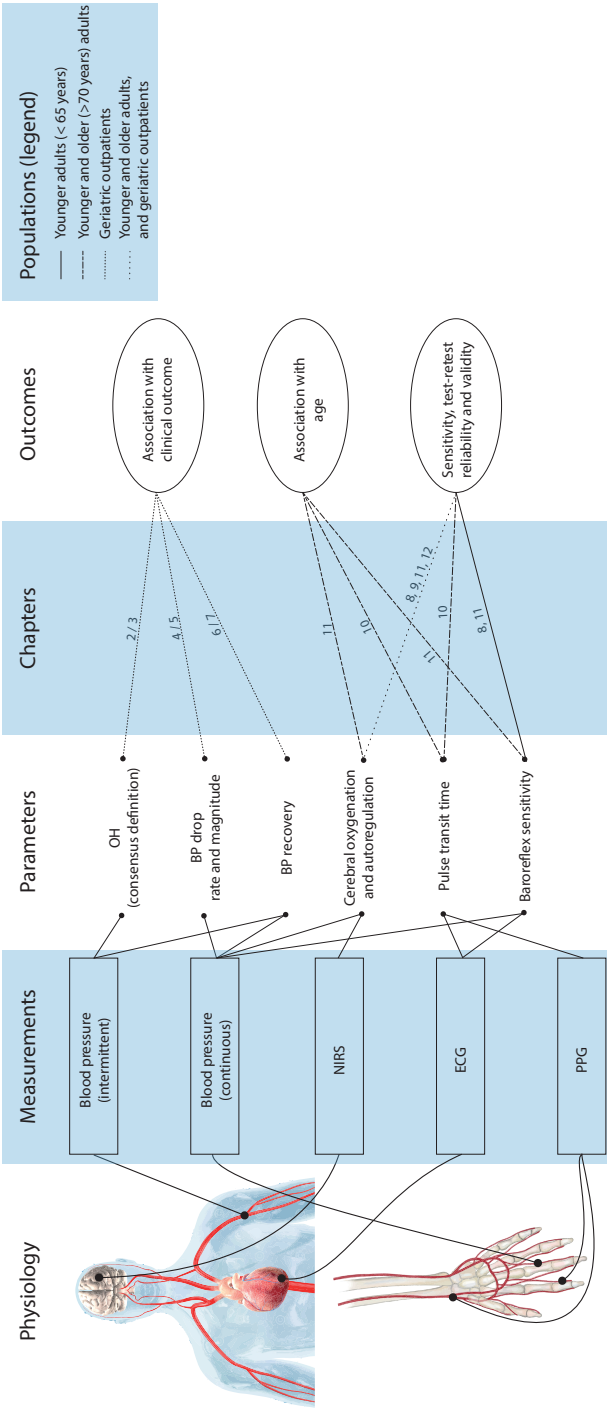


Figure 1.2. Overview of the measurements, extracted parameters and thesis chapters relating these parameters to outcomes. NIRS: near-infrared spectroscopy; ECG: electrocardiography; PPG: photoplethysmography; OH: orthostatic hypotension; BP: blood pressure.

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Part I

The clinical value of the orthostatic hypotension consensus definition

Chapter 2

Orthostatic hypotension and physical functioning in older adults: A systematic review and meta-analysis

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Ageing Research Reviews. 48, 122–144 (2018).

Abstract

Orthostatic hypotension (OH) may negatively affect physical functioning and aggravate morbidities, but existing evidence is contradictory. A systematical search was conducted for studies on the association of OH and physical functioning in older adults, categorized as: balance performance, gait characteristics, walking speed, Timed Up and Go time, handgrip strength, physical frailty, exercise tolerance, physical activity, activities of daily living (ADL), and performance on the Hoehn and Yahr scale (HY) and Unified Parkinson's Disease Rating Scale (UPDRS). Forty-two studies were included in the systematic review (29,421 individuals) and 29 studies in the meta-analyses (23,879 individuals). Sixteen out of 42 studies reported a significant association of OH with worse physical functioning. Meta-analysis showed a significant association of OH with impaired balance performance, ADL performance and HY/UPDRS III performance. These results highlight the need to invest in OH interventions to potentially improve physical functioning.

Introduction

Orthostatic hypotension (OH) is a serious disorder, associated with increased risk of cardiovascular disease, impaired renal function, dementia, falls, and death.[1–5] OH is defined as a systolic blood pressure drop of at least 20 mmHg and/or a diastolic blood pressure drop of at least 10 mmHg within 3 minutes after standing up according to the consensus definition.[6] The prevalence of OH was reported to range from 9-30% in community-dwelling adults aged above 65 years[4,7] to more than 50% in nursing home residents.[8] OH is particularly prevalent in patients with Parkinson's Disease (PD, 47-58%).[9,10]

OH may negatively affect physical functioning (e.g. balance performance, gait characteristics, walking speed, exercise tolerance and activities of daily living (ADL)) in older adults through different mechanisms: 1) acute decreased brain perfusion and oxygenation within minutes after postural change; [11] 2) chronic brain pathology, such as brain atrophy, microbleeds and white matter brain lesions;[12–14] 3) impaired muscle microcirculation, causing poor muscle endurance and pain in neck, buttock and calf muscles.[15–18] Therefore, OH may cause deterioration of physical functioning. However, evidence on the association of OH and physical functioning in older adults is contradictory, as an association with both impaired[19,20] and better[21] physical functioning was reported.

To obtain insight in the clinical relevance of OH, this systematic review and meta-analysis provides a summary of the existing evidence on the association of OH and physical functioning in older adults.

Methods

The review protocol was registered in the PROSPERO International prospective register of systematic reviews (CRD42017060134). MEDLINE (from 1946), PubMed (from 1966) and EMBASE databases (from 1947) were systematically searched for studies published until February 2017 and investigating OH and physical functioning in cohorts of older adults (> 65 years). The search strategy is presented in supplementary file S2.1 and includes the keywords 'orthostatic hypotension', 'balance', 'gait', 'mobility', 'walking', 'strength', 'exercise' and 'activity'.

Study selection

After removing duplicates, studies were assessed for potential eligibility by two different reviewers (AM and PTSBH) by screening titles and abstracts. Potentially eligible studies were then screened full-text by the same reviewers. Studies were considered eligible if the following criteria were met: 1) publication in English, 2) mean or median age of the study cohort was 65 years or higher, 3) blood pressure was assessed before and after postural change and 4) its association with physical functioning was assessed. Conference abstracts, reviews, editorials and letters to the editor were excluded. Any disagreements between the reviewers were resolved by discussion with a third author (EMR, CGM or ABM). If study results from the same cohort were published in duplicate, one study was included in the systematic review. The references of eligible studies were screened for additional studies meeting the criteria.

Data extraction and study quality

The following data were extracted independently by two authors (AM and PTSBH): first author; year of publication; size, age and sex of the included population; study design; study population; OH definition; OH test conditions (i.e. duration of resting period before postural change and type of postural change); blood pressure measurement (continuous or intermittent) and timing; OH prevalence; assessment method of physical functioning; physical functioning.

Study quality of the included studies was assessed independently by two authors (AM and PTSBH) using the nine-point Newcastle Ottawa Scale,[22] higher scores indicating lower risk of bias. Studies with scores of 0-3, 4-6 and 7-9 points were considered low, moderate and high quality, respectively. The specified Newcastle Ottawa Scale for this study is provided in supplementary file S2.2.

Data selection

Data on the consensus definition of OH (systolic blood pressure drop > 20 mmHg or diastolic blood pressure drop > 10 mmHg) or systolic OH (systolic blood pressure drop > 20 mmHg) were used if different definitions for OH were used in one study.[6] Continuously measured blood pressure was used rather than intermittently measured

blood pressure, as continuous blood pressure measurements are more sensitive for the diagnosis of OH.[23,24] Results of active stand tests rather than other types of postural change (e.g. head up tilt test) were used. In studies reporting different balance test outcomes for the same population, objective tests were used rather than subjective tests and challenging tests rather than easier tests (e.g. tandem stance rather than side-by-side stance). In three studies, results were only depicted in figures. The authors of these studies were contacted for the exact results, two of whom responded.[24,25] In the other case, we extracted data from the figures.[26] Study populations were categorized as community-dwelling adults, outpatients, geriatric inpatients, nursing home residents or patients with PD or parkinsonism (i.e. atypical parkinsonism or multiple system atrophy).

Physical functioning categories

Physical functioning was grouped in 12 categories: 1) balance performance (i.e. self-reported or objectively assessed balance performance), 2) gait characteristics (i.e. gait initiation, symmetry, gait regularity, trunk sway and path width assessed by a healthcare professional), 3) mobility (i.e. self-reported mobility and use of walking aids), 4) walking speed (i.e. walking speed on test path length between 4m - 500m), 5) Timed Up and Go time (TUG, i.e. time needed to stand up, walk around a cone and sit down), 6) handgrip strength (HGS, i.e. hand grip strength of strongest hand), 7) physical frailty (i.e. frailty assessed using the Fried frailty scale), 8) exercise tolerance (i.e. peak O_2 consumption during exercise or performance on exercise scale for specific diseases), 9) physical activity (i.e. self-reported time spent non-sedentary), 10) activities of daily living (ADL) performance (i.e. self-reported ADL independence), 11) UPDRS II ADL performance (i.e. performance on the ADL subscale of the Unified Parkinson's Disease Rating Scale (UPDRS II)), and 12) HY / UPDRS III performance (i.e. performance on the Hoehn and Yahr (HY) or UPDRS III scales, assessing motor performance in Parkinson's Disease).

Meta-analysis

Data were pooled if 1) studies had the same study design (i.e. cross-sectional versus longitudinal); 2) physical functioning was reported for subjects with OH compared to those without OH using odds ratio's (ORs), means, medians or the prevalences of the OH and the non-OH group; 3) the reported physical function outcome could be classified into one physical functioning category.

For dichotomous physical functioning outcomes, the unadjusted odds ratio (OR) was used or the OR was computed from reported prevalence data in the group with and without OH. For continuous physical functioning outcomes, the means and standard deviations (SD) were used to compute standardized mean differences and the logarithm of the OR (logOR), to enable pooling with dichotomous outcomes

according to the Hasselblad and Hedges method.[27,28] Medians, ranges or interquartile ranges were converted to means and SDs[29] in studies with more than 50 subjects.[30]

Meta-analyses, including at least two studies, were performed using Review Manager (RevMan. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A random effects model was used, as studies were different with respect to the used OH definition, blood pressure measurement protocol and physical functioning measurement, implying heterogeneity.[31] Apart from the pooled analyses per category of physical functioning, subgroup analyses were performed per population. Heterogeneity was expressed using the I^2 statistic (<25% low; < 50%: moderate; > 50%: high). A sensitivity analysis excluding low quality studies was performed. P-values below 0.05 and 0.1 were considered significant and a trend, respectively. An estimate of publication bias was calculated using Egger's test for meta-analyses including at least ten studies, using a significance level of 10%.[32,33]

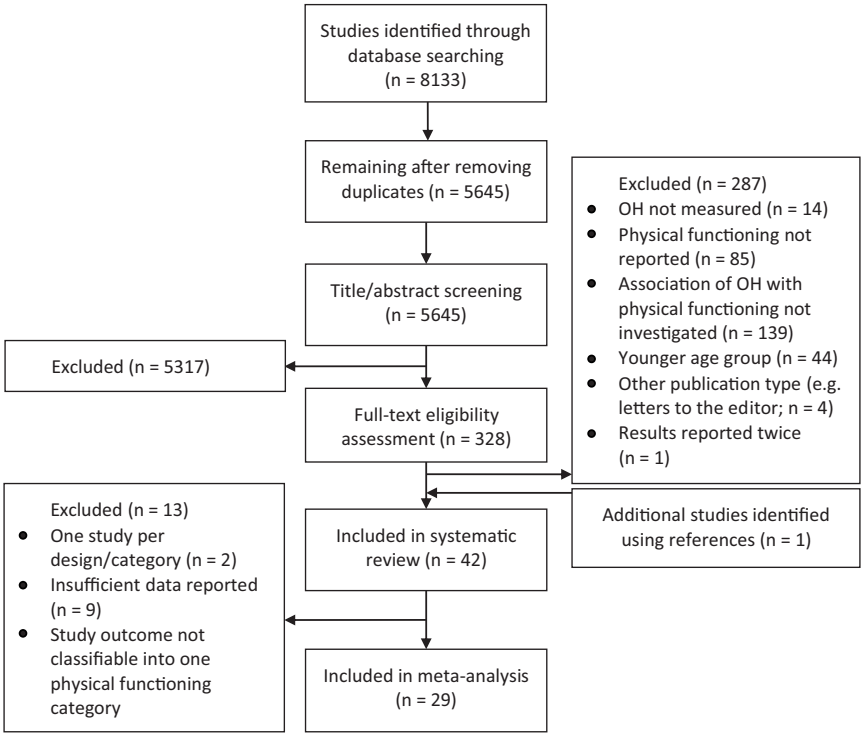


Figure 2.1. Study identification and selection.

Table 2.1. Study characteristics, stratified by population

First author, year of publication	N	Mean age (SD or range)	Male (%)	Design	OH definition	Resting period (min)	Postural change	BP measure-ment	BP timing (min)	Included in meta-analysis
Community-dwelling										
Ensrud, 1992[19]	9704	71.7 (65-99)	0	Cs	sOH	5	AS	I	1	Yes
Formes, 2010[34]	19	67.5 (3.8)	63.5	Cs	NR	20	LBNP	C	36	No
Guo, 2003[35]	234	70	0	Cs	OH	NR	AS	NR	NR	No
	88			P	OH	NR	AS	NR	NR	No
Kobayashi, 2012[36]	86	73.1 (6.3)	24.4	Cs	OH	10	HUT	C	3	Yes
Mader, 1987[37]	300	69.8 (56-93)	23.0	Cs	sOH	5	AS	I	1	Yes
Masaki, 1998[38]	3741	(71-93)	100	Cs	OH	15	AS	I	3	No
Matsubayashi, 2017[20]	334	80.0 (5.0)	45.5	Cs	sOH	5	AS	I	1; 2	Yes
Rockwood, 2012[39]	1347	83.3 (6.4)	50.5	Cs	OH	NR	AS	I	< 3	Yes
Romero-Ortuno, 2011[40]	442	72	28	Cs	OH	10	AS	C	3	Yes
Rutan, 1992[41]	4931	64.3*	43.5	Cs	OH	NR	AS	I	3	Yes
Tang, 2012[42]	49	66.0 (7.0)	59	Cs	OH	10	PS	I	1-3†	No
Tilvis, 1996[43]	569	80.0 (4.1)	NR	Cs	OH	5	AS	I	1	No
Zhu, 2016[44]	364	74.6 (64-98)	49.5	Cs	OH	5	AS	I	1; 3	Yes
Outpatients										
Aydin, 2017[45]	290	74.8 (8.7)	40.7	Cs	OH	5	AS	I	3	Yes
Cordeiro, 2009[46]	91	74.4 (5.9)	34.1	Cs	NR	NR	AS	I	3	Yes
Gaxatte, 2017[47]	833	80.4 (7.4)	26.9	Cs	OH	10	AS	I	1; 3	Yes
Oishi, 2016[48]	64	84.0 (6.0)	31.3	Cs	OH	NR	AS	I	0; 1; 3; 5	Yes
Pasma, 2014[24]	58	80.6 (7.0)	43.1	Cs	OH or iOH	5	AS	C	3	Yes
Press, 2015[49]	571	83.0 (6.1)	35.9	Cs	OH	10	AS	I	1; 3	Yes
Soysal a, 2014[50]	546	73.3 (8.8)	39.4	Cs	OH	10	AS	I	1; 3	Yes
Soysal b, 2016[51]	407	75.1 (8.4)	37.3	Cs	OH	10	HUT	I	1; 3; 5	Yes
Susman, 1989[52]	100	73 (65-90)	38	Cs	OH	5	AS	I	1; 2	No
Geriatric inpatients										
Aries, 2012[53]	167	68.5 (15.2)	54.5	P	OH	3	AS	I	3	No
Bendini, 2007[54]	36	80.5 (6.2)	27.8	Cs	OH	NR	AS	I	1; 3	No
Coutaz, 2012[55]	340	80 (8.2)	31.5	Cs	OH	30	AS	I	1; 3; 5	Yes
Jodaitis, 2015[56]	285	85.0 (5.0)	46	R	OH	NR	SS	I	0; 1; 3	No

Kihara, 1998[57]	15	85.1 (2.1)	40	Cs	$OH_{30/15}$	NR	HUT	C	5	Yes
MacLennan, 1987[58]	100	82.4 (64-94)	0	Cs	sOH	NR	AS	NR	NR	Yes
Shen, 2015[59]	176	76.7 (6.6)	57.4	Cs	OH	5	AS	I	1; 3	Yes
Siennicki-Lantz, 1999[60]	27	82.2 (3.6)	0	Cs	sOH	NR	HUT	I	0-8†	No
Vloet, 2005[61]	85	80.0 (1.0)	51.7	Cs	sOH	5	AS	I	1; 3	Yes
Nursing home residents										
Gray-Miceli a, 2012[62]	77	90.0 (5.8)	18.0	Cs	OH	NR	NR	NR	NR	No
Gray-Miceli b, 2016[63]	47	90.7 (5.8)	26.0	Cs	OH	NR	NR	NR	NR	No
Ooi, 1997[21]	911	83.1 (10.9)	20.0	Cs	OH	NR	AS	I	1; 3	Yes
Patients with PD or parkinsonism										
Allcock, 2006[64]	159	70.6	61	Cs	OH	10	AS	I	NR	Yes
Ha, 2011[65]	1318	68.8 (30.7)	61.4	Cs	OH+	NR	AS	NR	NR	Yes
Hohler, 2012[66]	44	NR	61.4	Cs	OH	NR	SS	I	1; 3	Yes
Matinolli, 2009[67]	120	68.2 (10.1)	66.7	Cs	OH	NR	AS	I	1-3†	Yes
Matsui, 2006[68]	40	71.1 (8.3)	17.5	Cs	sOH	10	AS	I	0-3†	Yes
Merola, 2016[25]	121	66.7 (8.9)	57.0	Cs	OH	10	AS	I	1; 3	Yes
Perez-Lloret, 2012[69]	103	66.0 (1.0)	73	Cs	OH	5	AS	I	1-3†	No
Sithinamsuwan, 2010[70]	82	69.2 (10.3)	69.5	Cs	OH	5	AS	I	3	Yes

Cs: cross-sectional; P: prospective; R: retrospective; OH: consensus definition of orthostatic hypotension; $OH_{30/15}$: drop of 30 and 15 mmHg in systolic or mean blood pressure, respectively; OH+: OH with symptoms; iOH: initial OH (systolic blood pressure drop of at least 40 mmHg and/or a diastolic blood pressure drop of at least 20 mmHg within 15 seconds after standing); sOH: systolic blood pressure drop of at least 20 mmHg; NR: not reported; AS: active stand; SS: sit to stand; PS: passive sit; HUT: head up tilt; LBNP lower body negative pressure (i.e. a simulation of postural change); BP: blood pressure; C: continuous; I: intermittent; BP timing: time of blood pressure measurement after postural change. *percentage of population between 65 and 79 years. †measured with intervals of one minute.

Table 2.2. Prevalence of OH and associations of OH and physical functioning

First author	OH prevalence (%)	Balance	Gait characteristics	Mobility	Walking speed	TUG	HGS	Physical frailty	Exercise tolerance	Physical activity	ADL performance	UPDRS II	HY/UPDRS III
Community-dwelling													
Ensrud, 1992	14.0	.	.	.	.	.	.	.	.	.	+	.	.
Formes, 2010	.	.	.	.	.	.	.	.	=	.	.	.	.
Guo, 2003	11.4	++‡	.	++‡	++‡	.	.	.	.	.	.	.	.
Guo, 2003	.	=‡	.	=‡	=‡	.	.	.	.	.	.	.	.
Kobayashi, 2012	33.7	.	.	.	=	.	=	.	.	.	.	.	.
Mader, 1987	10.7	=	.	.	.	.	.	.	.	.	.	.	.
Masaki, 1998	6.9	.	.	.	++	.	++	.	.	.	.	.	.
Matsubayashi, 2017	6.6	.	.	.	.	=	.	.	.	.	+	.	.
Rockwood, 2012	28.9	.	.	.	.	.	.	=	.	.	.	.	.
Romero-Ortuno, 2011	94.1	.	.	.	=	.	=	=	.	=	.	.	.
Rutan, 1992	16.2	=§	.	+	.	.	.	.	.	.	=	.	.
Tang, 2012	14.2	.	.	.	.	.	.	.	=	.	.	.	.
Tilvis, 1996	21.4	.	.	.	.	.	.	.	=	.	.	.	.
Zhu, 2016	11.0	.	.	=	.	.	.	.	.	=	.	.	.
Outpatients													
Aydin, 2017	37.0	=	=	.	.	.	.	.	.	.	=	.	.
Cordeiro, 2009	29.1	+	.	.	.	=	.	.	.	.	.	.	.
Gaxatte, 2017	23.9	=	=	.	.	=	.	.	.	.	+	.	.
Oishi, 2016	26.6	=	.	.	.	--	.	.	.	.	.	.	.
Pasma, 2014	57.0	+	.	.	.	.	.	.	.	.	.	.	.
Press, 2015	32.2	.	.	.	.	.	.	.	.	.	=	.	.
Soysal a, 2014	27.5	=	=	.	.	.	.	.	.	.	=	.	.
Soysal b, 2016	22.1	=	.	.	.	.	.	.	.	.	.	.	.
Susman, 1989	31.0	.	.	.	.	.	.	.	.	.	=	.	.
Geriatric inpatients													
Aries, 2012	13.1	.	.	.	.	.	.	.	.	.	=	.	.
Bendini, 2007	25.0	.	.	.	.	.	.	.	.	.	+	.	.
Coutaz, 2012	42.4	.	.	.	.	.	.	.	.	.	=	.	.
Jodaitis, 2015	41.0	.	.	.	.	.	.	.	.	.	=	.	.
Kihara, 1998	40.0	.	.	.	.	.	.	.	.	.	=	.	.
MacLennan, 1987	34.7	.	.	=	.	.	.	.	.	.	.	.	.
Shen, 2015	20.5	++	=	=	=	.	=	.	.	.	.	.	.
Siennicki-Lantz, 1999	48.1	.	.	.	.	.	.	.	.	.	=	.	.
Vloet, 2005	56.5	.	.	=	.	.	.	.	.	.	.	.	.
Nursing home residents													
Gray-Miceli a, 2012	9.3	++	.	.	.	.	.	.	.	.	.	.	.
Gray-Miceli b, 2016	15.4	+	++	.	.	.	.	.	.	.	.	.	.
Ooi, 1997	51.5	.	.	--	.	.	.	.	.	.	=	.	.
Patients with PD or parkinsonism													
Allcock, 2006	50.3	.	.	.	.	.	.	.	.	.	.	.	=
Ha, 2011	19.0	.	.	.	.	.	.	.	.	.	.	.	+‖
Hohler, 2012	39.0	+	.	.	=	=	.	.	.	.	+	.	.
Matinolli, 2009	52.5	.	.	=	=	=	.	.	.	=	.	=	=
Matsui, 2006	62.5	.	.	.	.	.	.	.	.	.	.	.	=
Merola, 2016	30.6	.	.	+	.	.	.	.	.	.	+	+	=
Perez-Lloret, 2012	36.9	.	.	.	.	.	.	.	.	.	.	=#	=#
Sithinamsuwan, 2010	40.2	.	.	.	.	.	.	.	.	.	.	.	+

Results are denoted with '++' ($p < 0.01$) or '+' ($p<0.05$) if OH was associated with worse physical functioning, '=' if no association was found, '--' ($p < 0.05$) if OH was associated with better physical functioning and '.' if no data was available. *Cross-sectional analysis. †Prospective analysis. ‡Results from a combined task involving walking speed, balance performance and mobility. §Adjusted result shown is not significant, but unadjusted result is significant. #This association was only found for the subgroup of patients with PD. ‖Combined UPDRS II and III scales.

Results

Figure 2.1 shows the study identification and selection flowchart. The search resulted in 5,645 studies. Of these studies, 328 full text articles were retrieved and screened for study eligibility. Forty-two studies were included in the systematic review. Data extracted from 29 studies were included in a meta-analysis.

Systematic review

Table 2.1 provides the study characteristics of each included study. The studies included a total of 29,421 individuals. Thirty-nine studies were cross-sectional, 2 were prospective and 1 was retrospective. Community-dwelling populations were investigated in 13 studies, outpatients in 9 studies, geriatric inpatients in 9 studies, nursing home residents in 3 studies and patients with PD or parkinsonism in 8 studies. Thirty studies used the consensus definition of OH, 7 studies used systolic OH and 5 studies used other OH definitions.

Table 2.2 presents an overview of the associations of OH and physical functioning. The extracted data are provided in supplementary table S2.3. OH was associated with physical functioning in 18/43 of the studies: impaired balance (7/14), gait abnormalities (1/5), mobility (worse: 3/9, better: 1/9), slower walking speed (2/7), TUG time (slower: 0/6, faster: 1/6) and lower HGS (1/4). Associations between OH and physical frailty, exercise tolerance or physical activity were significant in none of the studies. OH was associated with worse physical functioning in 6/17 of the studies assessing ADL performance, 1/3 of the studies using the UPDRS II ADL scale and 2/7 of studies using the HY/UPDRS III performance scale.

Table 2.3 presents the study quality for all included studies. Nineteen studies were of low quality, 23 studies were of moderate quality and none of the studies were of high quality.

Meta-analysis

A total of 23,879 individuals from 29 cross-sectional studies were included in the meta-analyses. None of the longitudinal studies were included. Nineteen of the included studies used the consensus definition of OH, 6 studies used the systolic OH definition and 4 studies used other definitions. Supplementary table S2.4 shows the list of physical functioning measures per physical functioning category.

Figure 2 shows the overall pooled effect estimates of the association of OH with physical functioning stratified by physical functioning categories. OH was significantly associated with balance impairment in all populations (figure 3, OR 0.57, 95% CI 0.42-0.78). OH was not associated with gait characteristics, mobility, walking speed, TUG, HGS, physical frailty and physical activity (figure 4-10). OH was significantly associated with impaired ADL performance (figure 11, OR 0.63, 95% CI 0.45-0.88), but not with UPDRS II ADL performance (figure 12, OR 0.41, 95% CI 0.14-1.21). OH was significantly associated with worse HY/UPDRS III performance (figure 13, OR

Table 2.3. Study quality assessed using the Newcastle Ottawa Scale

First author	Representativeness of cohort	Non-exposed cohort from same community	BP measured continuously	Consensus definition of OH	Adjusted for age/sex	Adjusted for other factors	Objective outcome	Follow up > 6 months	< 20% loss to follow up	Total score
Community-dwelling										
Ensrud, 1992	*	*	-	-	*	-	-	-	-	3
Formes, 2010	*	-	*	-	-	-	-	-	-	2
Guo, 2003	*	*	-	*	-	-	*	*	-	5
Kobayashi, 2012	*	*	*	*	-	-	*	-	-	5
Mader, 1987	*	*	-	-	-	-	-	-	-	2
Masaki, 1998	*	-	-	*	-	-	*	-	-	3
Matsubayashi, 2017	*	*	-	-	-	-	*	-	-	3
Rockwood, 2012	*	*	-	*	-	-	*	-	-	4
Romero-Ortuno, 2011	*	*	*	*	-	-	*	-	-	5
Rutan, 1992	*	*	-	*	*	*	-	-	-	5
Tang, 2012	*	*	-	*	-	*	*	-	-	5
Tilvis, 1996	*	*	-	*	*	-	*	-	-	5
Zhu, 2016	*	*	-	*	-	-	-	-	-	3
Outpatients										
Aydin, 2017	*	*	-	*	-	-	*	-	-	4
Cordeiro, 2009	*	*	-	-	-	-	*	-	-	3
Gaxatte, 2017	*	*	-	*	-	-	*	-	-	4
Oishi, 2016	*	*	-	*	-	-	*	-	-	4
Pasma, 2014	*	-	*	*	*	-	*	-	-	5
Press, 2015	*	*	-	*	-	-	-	-	-	3
Soysal a, 2014	*	*	-	*	-	-	*	-	-	4
Soysal b, 2016	*	*	-	*	-	-	*	-	-	4
Susman, 1989	*	*	-	*	-	-	-	-	-	3
Geriatric inpatients										
Aries, 2012	*	-	-	*	-	-	*	-	-	3
Bendini, 2007	*	-	-	*	*	-	-	-	-	3
Coutaz, 2012	*	*	-	*	-	-	*	-	-	4
Jodaitis, 2015	*	*	-	*	-	*	-	-	-	4
Kihara, 1998	*	-	*	-	-	-	-	-	-	2
MacLennan, 1987	*	*	-	-	-	-	*	-	-	3
Shen, 2015	*	*	-	*	*	-	*	-	-	5
Siennicki-Lantz, 1999	*	*	-	-	-	-	-	-	-	2
Vloet, 2005	*	*	-	-	-	-	-	-	-	2
Nursing home residents										
Gray-Miceli a, 2012	*	*	-	*	-	-	*	-	-	4
Gray-Miceli b, 2016	*	*	-	*	-	-	-	-	-	3
Ooi, 1997	*	*	-	*	*	*	-	-	-	5
Patients with PD or parkinsonism										
Allcock, 2006	*	-	-	*	-	-	*	-	-	3
Ha, 2011	*	*	-	-	-	-	*	-	-	3
Hohler, 2012	*	*	-	*	-	-	*	-	-	4
Matinolli, 2009	*	*	-	*	-	-	*	-	-	4
Matsui, 2006	*	*	-	-	-	-	*	-	-	3
Merola, 2016	*	*	-	*	-	*	*	-	-	5
Perez-Lioret, 2012	*	*	-	*	*	*	*	-	-	6
Sithinamsuwan, 2010	*	*	-	*	-	-	*	-	-	4

* Indicates an attributed point. BP: blood pressure.

0.67, 95% CI 0.54-0.82). Exclusion of 19 low quality studies from the meta-analyses did not change the significance of the associations of OH with any of the physical functioning categories, except for HY/UPDRS III performance (3 studies remaining; OR 0.65, 95 % CI 0.34-1.19).

Heterogeneity and publication bias

Heterogeneity was high for the results of balance performance, mobility, ADL performance and UPDRS II ADL performance; moderate for TUG; and low for gait characteristics, walking speed, HGS, physical frailty, physical activity, and HY and UPDRS III performance. Egger's regression test for balance performance and ADL performance showed statistical evidence for publication bias of ADL performance (p = 0.972 and p = 0.045, respectively).

Discussion

Less than half of studies included in the systematic review showed an association between OH and physical functioning. In the meta-analyses, a significant association of OH with impaired balance performance was found, whereas OH was not associated with gait characteristics, mobility, walking speed, TUG, HGS, physical frailty and physical activity. OH was associated with impaired ADL and HY/UPDRS III performance, but not with UPDRS II ADL performance. Most studies were of moderate quality.

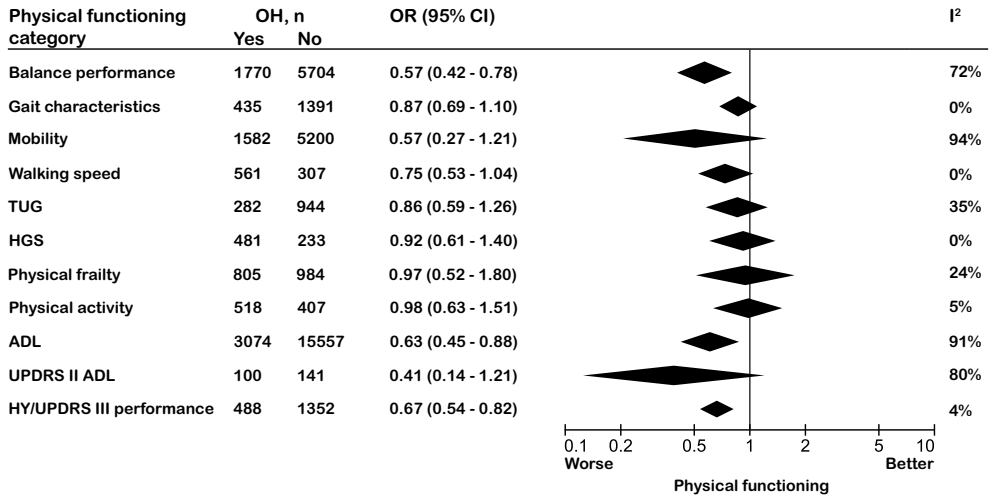
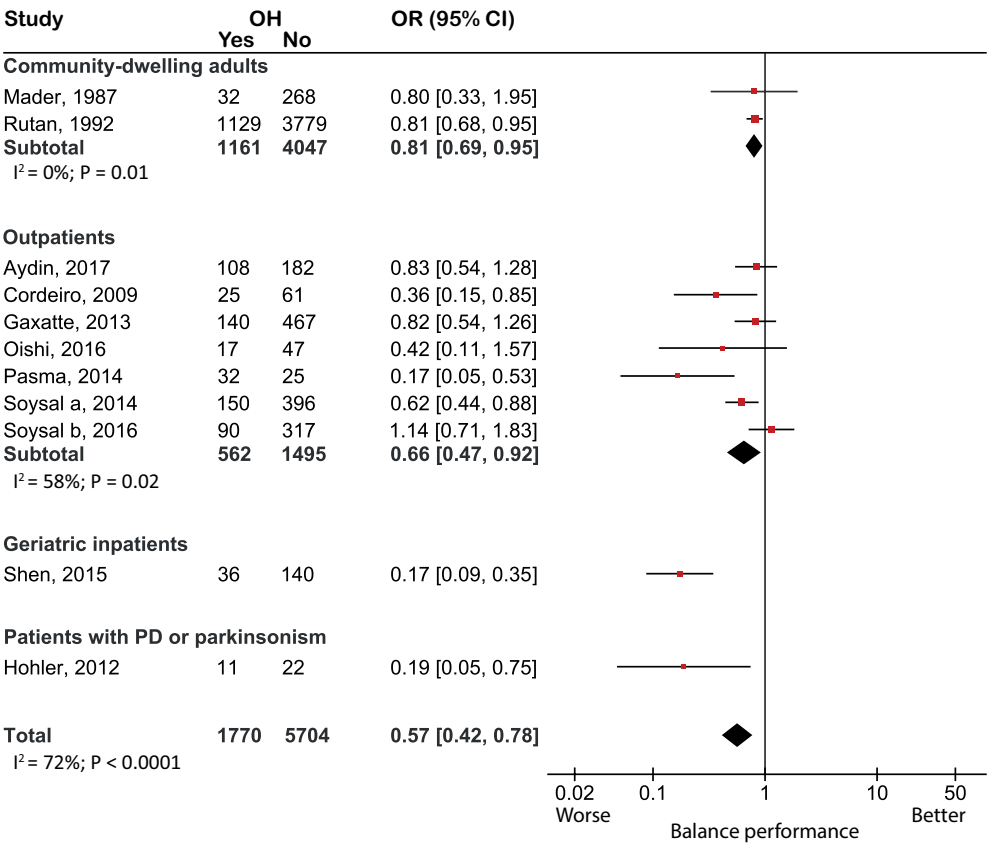
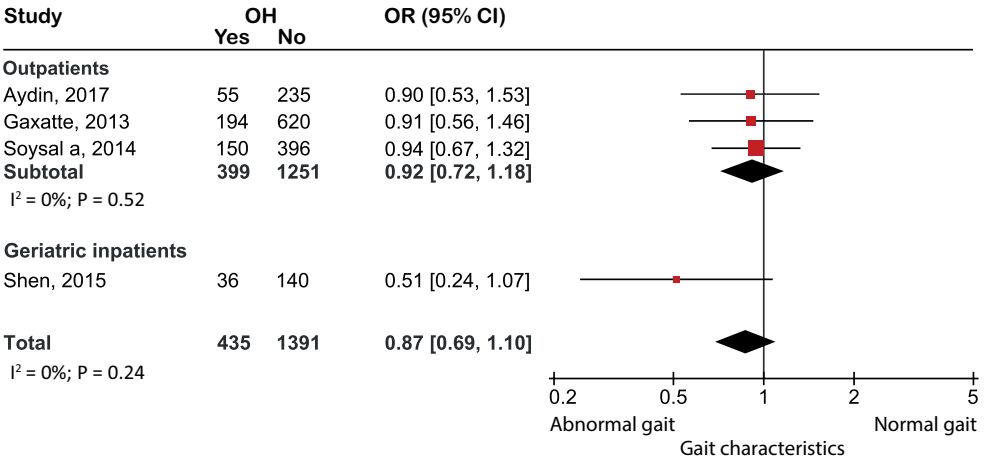


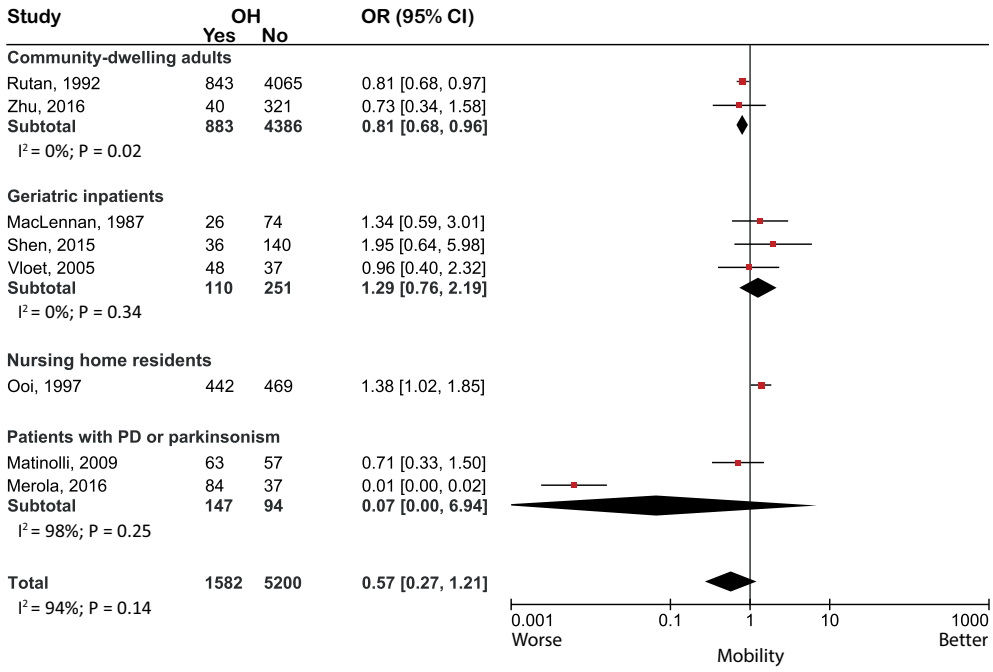
Figure 2.2. Pooled estimates of the association of OH and physical performance, per physical functioning category. TUG: Timed Up and Go; HGS: handgrip strength; ADL: activities of daily living; UPDRS: Unified Parkinson's Disease Rating Scale; HY: Hoehn and Yahr Scale.



^ **Figure 2.3.** Forest plot of studies investigating OH and balance performance. PD: Parkinson's disease.

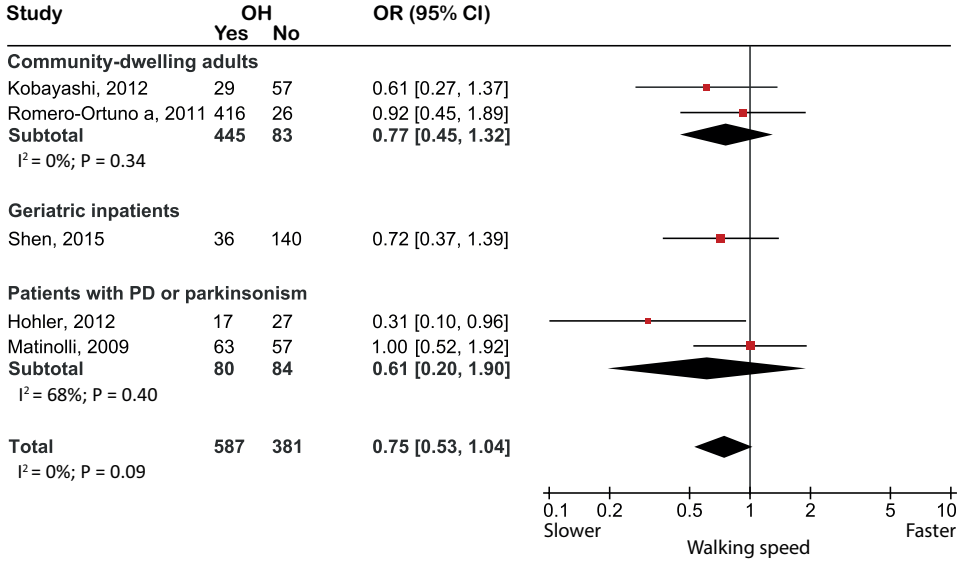
v **Figure 2.4.** Forest plot of studies investigating OH and gait characteristics.

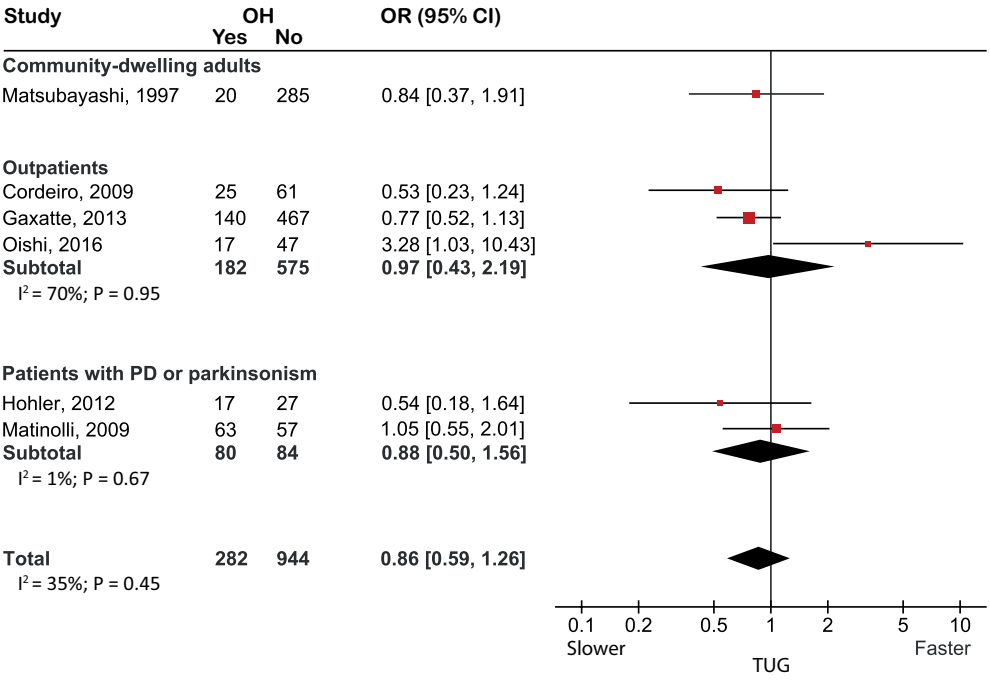




^ **Figure 2.5.** Forest plot of studies investigating OH and mobility. PD: Parkinson's disease.

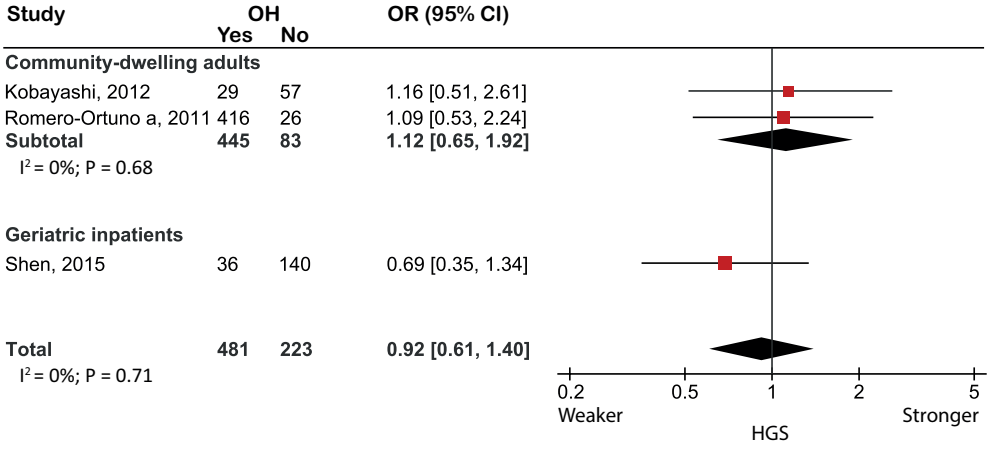
v **Figure 2.6.** Forest plot of studies investigating OH and walking speed. PD: Parkinson's disease.





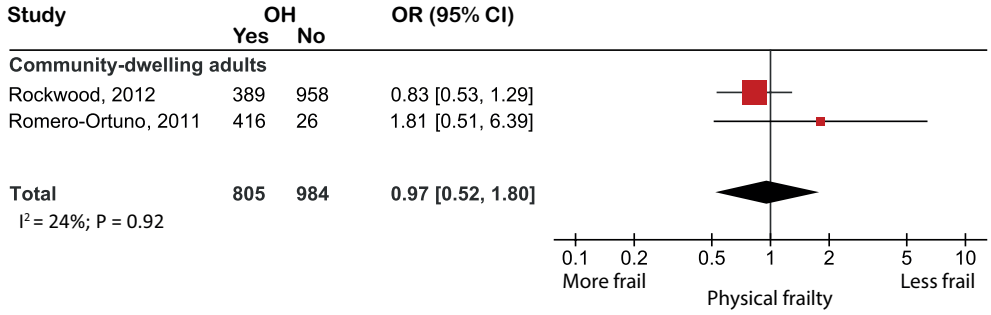
^ Figure 2.7. Forest plot of studies investigating OH and Timed Up and Go (TUG) time. PD: Parkinson's disease.

v Figure 2.8. Forest plot of studies investigating OH and hand grip strength (HGS).



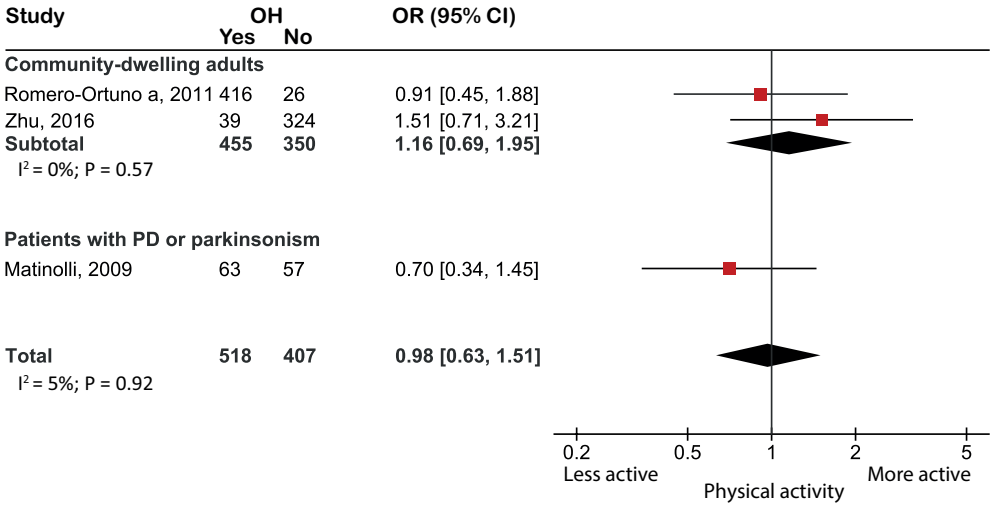
To the best of our knowledge, this is the first systematic review and meta-analysis addressing the association between OH and physical functioning in older adults. Previous reviews on OH reported an association with falls and mortality.[71–73] The association of OH with physical functioning was modest, showing significant associations only in some physical functioning categories. As no more than one longitudinal study was available per physical functioning category, no longitudinal studies were included in the meta-analysis.

The significant association of OH and impaired balance performance is in line with a previous study reporting an association between OH and a shorter time to a first fall, suggesting impaired balance performance as a possible mechanism.[72] The association found in the present study was robust due to the large number of individuals included in the meta-analysis and the congruence of most studies with respect to the direction of the effect.



^ **Figure 2.9.** Forest plot of studies investigating OH and physical frailty.

v **Figure 2.10.** Forest plot of studies investigating OH and physical activity. PD: Parkinson's disease.



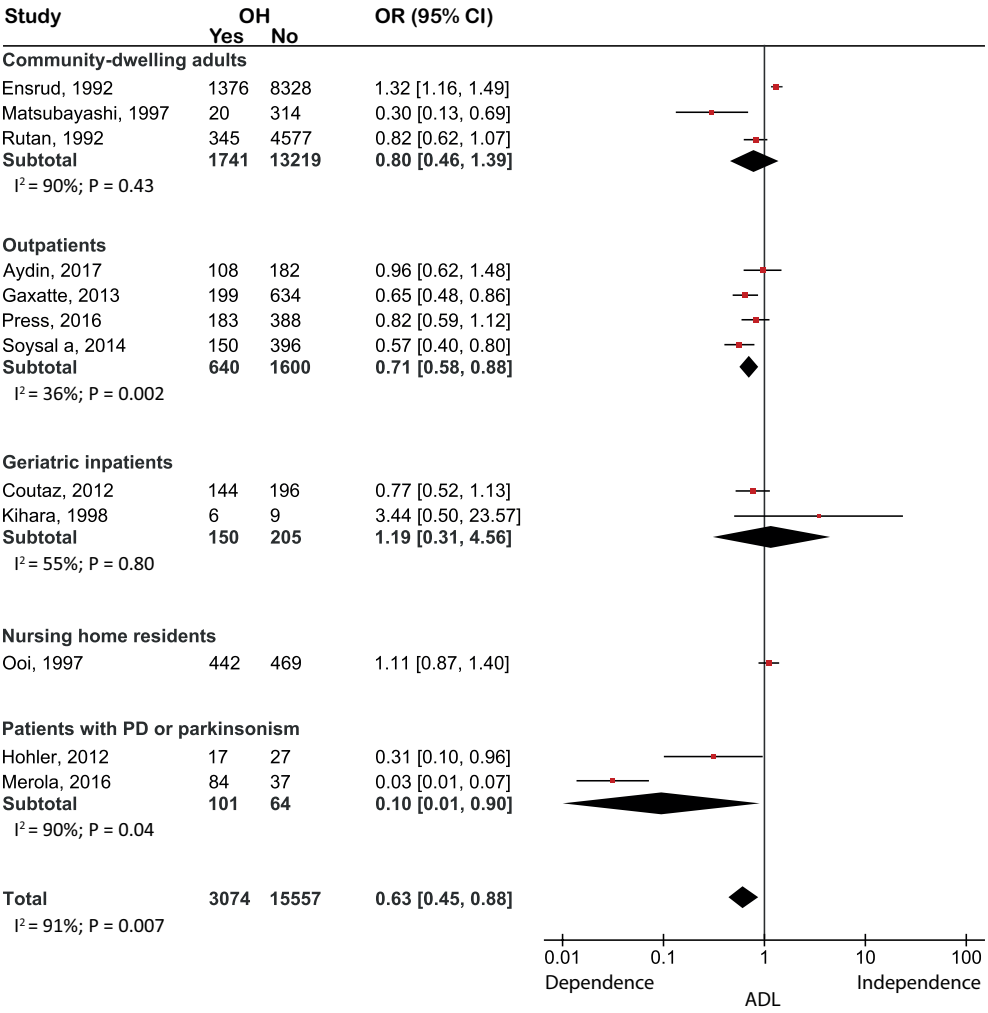
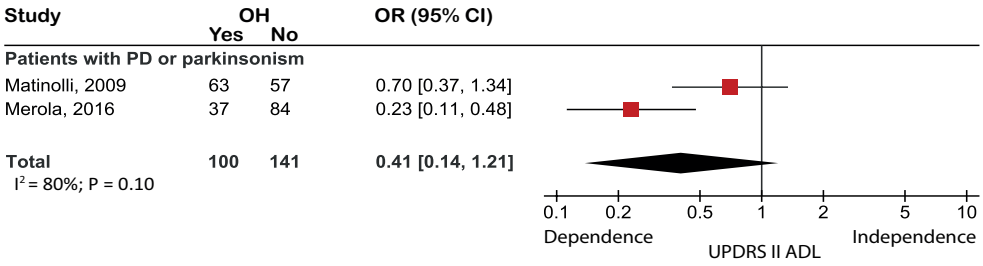


Figure 2.11. Forest plot of studies investigating OH and activities of daily living (ADL). PD: Parkinson's disease.

No association of OH was found with gait characteristics, mobility, walking speed and TUG, HGS, physical frailty and physical activity, which may be explained by the large study diversity and poorly standardized measurement protocols with respect to OH definition, blood pressure measurement protocol and physical functioning outcome, and by a moderate overall study quality.

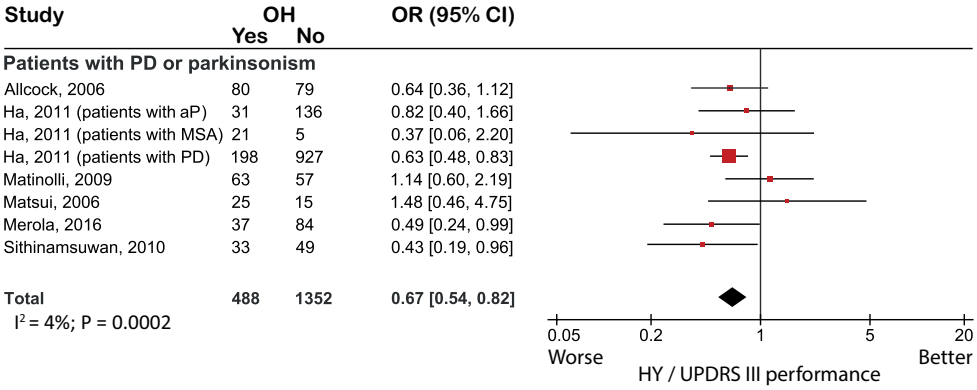
OH was significantly associated with impaired ADL performance in the meta-analysis, which included a large number of individuals. However, results on Egger's test indicate that this association may have been influenced by publication bias, suggesting exclusion of negative studies.

The found association of OH with HY/UPDRS III performance should be



^ Figure 2.12. Forest plot of studies investigating OH and activities of daily living (ADL) performance using the Unified Parkinson's Disease Rating (UPDRS) II scale. PD: Parkinson's disease.

v Figure 2.13. Forest plot of studies investigating OH and performance on Hoehn and Yahr (HY) or Unified Parkinson's Disease Rating Scale (UPDRS) III scale. aP: atypical parkinsonism; MSA: multiple system atrophy; PD: Parkinson's disease.



interpreted cautiously, as it did not remain significant after exclusion of low-quality studies.

Potential pathophysiological mechanisms involved

This study provides indications about potentially involved pathophysiological mechanisms. White matter brain lesions are associated with OH[12–14] and may lead to impaired balance performance.[12,74] They are also associated with cognitive impairment,[75,76] which might be an intermediate factor between OH and impaired ADL performance, as cognitive impairment is associated with both OH and impaired ADL performance.[77–83] No association of OH was found with TUG, the only category involving a standardized postural change, suggesting OH does not affect physical functioning largely by acute mechanisms. However, as blood pressure and TUG were not assessed simultaneously, it is unknown whether individuals diagnosed with OH had a blood pressure drop during TUG assessment. A common neural degenerative

process may underlie the association of OH with HY/UPDRS III performance, as PD both affects the autonomic system, causing OH, and the dopaminergic neurons in the nigrostriatal system, causing worse HY/UPDRS III performance.[84,85]

Strengths and limitations

The strength of this systematic review is that data were reported on a variety of physical functioning categories and analyses were stratified for different populations. However, the diversity of studies within categories of physical functioning has increased the heterogeneity. The overall quality of the included studies was moderate and, as non-adjusted data were included in the meta-analyses, a confounding role of age, sex, height and other factors cannot be excluded. No conclusions can be drawn about the longitudinal association of OH with physical functioning and potential causality underlying the found associations.

Conclusion

This systematic review and meta-analysis shows that OH is associated with impaired balance performance, ADL performance and HY/UPDRS III performance, but not with other categories of physical functioning, based on studies with overall moderate quality. Standardized OH and physical functioning measurement protocols are needed to enable more accurate investigation of the relationship between OH and physical functioning. Future research should investigate the role of OH as a predictor of physical functioning decline in longitudinal studies and address the effect of OH interventions to potentially improve physical functioning.

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Supplementary material

Supplementary file S2.1. Search strategy

MEDLINE search strategy
1 exp Hypotension, Orthostatic/ (5281)
2 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).kf. (407)
3 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).tw. (6866)
4 or/1-3 (9329)
5 (Exercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).tw. (585748)
6 (Exercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).kf. (20955)
7 exp exercise/ or exp exercise test/ or exp exercise tolerance/ or exp physical endurance/ or exp physical fitness/ or exp walk test/ or exp muscle strength/ or exp hand strength/ or exp gait/ or exp postural balance/ or exp “activities of daily living”/ or exp geriatric assessment/ or exp frail elderly/ or exp Accidental Falls/ (345254)
8 or/5-7 (846790)
9 4 and 8 (1695)
10 exp Hypotension, Orthostatic/ (5281)
11 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).kf. (407)
12 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).tw. (6866)
13 or/10-12 (9329)
14 (Exercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).tw. (585748)
15 (Exercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).kf. (20955)
16 exp exercise/ or exp exercise test/ or exp exercise tolerance/ or exp physical endurance/ or exp physical fitness/ or exp walk test/ or exp muscle strength/ or exp hand strength/ or exp gait/ or exp postural balance/ or exp “activities of daily living”/ or exp geriatric assessment/ or exp frail elderly/ or exp Accidental Falls/ (345254)
17 or/14-16 (846790)
18 13 and 17 (1695)

PubMed search strategy
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EMBASE search strategy
1 exp falling/ (32186)
2 exp orthostatic hypotension/ or exp orthostatic stress/ or exp orthostatic blood pressure/ (19527)
3 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).kw. (1449)
4 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).tw. (9595)
5 or/2-4 (22485)
6 exp physical performance/ or exp physical mobility/ or exp "physical activity, capacity and performance"/ or exp exercise/ or exp exercise test/ or exp body equilibrium/ or exp endurance/ or exp fitness/ or exp hand strength/ or exp muscle strength/ or exp grip strength test/ or exp balance impairment/ or exp daily life activity/ or exp activity of daily living assessment/ or exp geriatric assessment/ or exp frail elderly/ or exp falling/ (994777)
7 (Excercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).tw. (718598)
8 (Excercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).kw. (53323)
9 or/6-8 (1523611)
10 5 and 9 (5009)

Supplementary file S2.2. Specified Newcastle Ottawa Scale

Note: A study can be given a maximum of one point for each numbered item within the Selection and Outcome categories. A maximum of two points can be given for Comparability

Selection (S)

1. Representativeness of the exposed cohort with orthostatic hypotension
    a. Subjects representative of the average subjected aged 65 years and older with orthostatic hypotension *
    b. Not representative or no description
2. Selection of the non-exposed cohorts: subjects without orthostatic hypotension from the same community
    a. Yes *
    b. No
    c. No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure: how is orthostatic hypotension diagnosis made
    a. Blood pressure measured both continuously and intermittently *
    b. Blood pressure was measured continuously *
    c. Blood pressure measured intermittently
    d. No description or unclear
4. How was orthostatic hypotension defined?
    a. Based on consensus definition of OH (SBP drop > 20 mmHg or DBP drop > 10 mmHg) *
    b. Other
    c. Not specified

Comparability (C)

1. Comparability of cohorts adjusted for potential confounders with respect to physical functioning
    a. The study controls for: age, sex or both*
    b. Study controls for any other factors, e.g. medication (e.g. antihypertensives, ACE inhibitors, beta blockers) and co-morbidities (e.g. Parkinson) *
    c. Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome (O)

1. Assessment of physical functioning outcome
    a. Objectively: by healthcare professional or measured using device *
    b. Self-reported retrospective
    c. No description
    d. Other
2. Was follow-up long enough
    e. Yes, > 6 months *
    f. No, < 6 months
    g. No follow up in study
3. Adequacy of follow-up of cohorts
    h. Complete follow up- all subjects accounted for *
    i. Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed *
    j. Follow up rate less than 80% and on description of those lost
    k. Not described or not applicable

SBP: systolic blood pressure; DBP: diastolic blood pressure; * = one point.

Supplementary table 2.3. Physical functioning data

First author	Physical functioning categories	Physical functioning data	Adjustments
Community-dwelling			
Ensrud, 1992	ADL	OH and impaired functional status (walking, climbing stairs, preparing meals, doing housework, shopping): OR 0.76 (CI 0.67-0.86)	Age
Formes, 2010	Exercise tolerance	No significant differences in MAP response to LBNP in group with high exercise tolerance (peak O2 uptake > 30ml/min/kg) compared to group with low exercise tolerance (peak O2 uptake 18-28 ml/min/kg)	-
Guo, 2003	Balance, mobility and walking speed	Movement time (s) on postural-locomotor-manual test: 2.39 (OH+), 2.26 (OH-), p < 0.01. Baseline OH not associated with performance on postural-locomotor-manual test after eight years.	Prospective results were adjusted for baseline performance on postural-locomotor-manual test.
Kobayashi, 2012	Walking speed; HGS	6-minute walk test (m): 498.4 (OH+, SD 80.4), 519.5 (OH-, SD 74.7), p = 0.972. HGS (kg): 26.7 (OH+, SD 7.7), 26.1 (OH-, SD 7.3), p = 0.559.	-
Mader, 1987	Balance	Postural symptoms (%; unsteadiness, dizziness) during standing: 21.9 (OH+), 18.3 (OH-), p > 0.05.	-
Masaki, 1998	Walking speed; HGS	Timed 10-foot walk (s): 4.79 (OH+), 4.31(OH-), p < 0.005. HGS (kg): 28.3 (OH+), 30.0 (OH-), p < 0.0001.	-
Matsubayashi, 2017	TUG; ADL	TUG (s): 16.4 (OH+, SD 4.5), 15.8 (OH-, SD 6.3), p > 0.05. ADL (walking, climbing stairs, eating, dressing, toileting, bathing, grooming and taking medicine; range from 0 [dependent] to 24 [independent]): 21.9 (OH+, SD 3.8) vs 23.2 (OH-, SD 1.8), p < 0.05.	-
Rockwood, 2012	Physical frailty	Fried frailty criteria (%): frail 8.0 (OH+), 6.7% (OH-), p = 0.058.	-
Romero-Ortuno, 2011	Walking speed; HGS; physical frailty; physical activity	Height normalized walking speed (m/s): 1.23 (OH+, SD 0.31), 1.22 (OH-, SD 0.22), p = 0.6. HGS (kg): 21.2 (OH+, SD 12.4), 20.6 (OH-, SD 11.9), p = 0.09. Fried frailty criteria (%): non-frail 44.0 (OH+), 57.7 (OH-), p = 0.17. pre-frail: 49.3 (OH+), 30.8 (OH-), p = 0.07, frail 6.7 (OH+), 11.5 (OH-), p = 0.41. Low physical activity (%): 17.5 (OH+), 11.5 (OH-), p = 0.39.	-
Rutan, 1992	Balance; mobility; ADL	OH prevalence (%): 20.7 (subjects with self-reported loss of balance), 17.4 (patients without loss of balance), OR = 1.18 (CI 0.99-1.40). OH prevalence (%): 22.3 (subjects with self-reported difficulty walking), 17.3 (subjects without difficulty walking), OR = 1.23 (CI 1.02-1.49). OH prevalence (%): 21.2 (subjects with self-reported ADL problems), 18.0 (subjects without ADL problems), OR 1.14 (CI 0.87-1.51).	Age and clinic site
Tang, 2012	Exercise tolerance	Peak VO2 consumption on graded max leg exercise test (ml/kg/min): 16.7 (OH-, SD 6.2), 18.1 (OH+, SD 8.3), p = 0.60.	Cholesterol and triglyceride levels
Tilvis, 1996	Exercise tolerance	Age- and sex adjusted prevalence of OH (%): 26.6 (subjects with NYHA class I, CI = 15.9-37.4), 40.1 (subjects with NYHA class III or IV, CI = 22.8-57.3).	Age and sex
Zhu, 2016	Mobility; physical activity	Need of walking aid in community (%): 25.0 (OH+), 16.6 (OH-). Physical activity during leisure (%): 74.4 (OH+), 65.7 (OH-).	-
Outpatients			
Aydin, 2017	Balance; gait; ADL	Tinetti balance score: 13.5 (OH-, SD 2.8), 13.2 (OH+, SD 3.2), p = 0.384. Tinetti gait score: 10.2 (OH-, SD 1.7), 10.1 (OH+, SD 1.8), p = 0.570. Basic activities of daily living score (0 - 100 [worst – best]): 91.5 (OH-, SD 13), 91.2 (OH+, SD 12.5), p = 0.856.	-
Cordeiro, 2009	Balance; TUG	Berg balance score: 50.48 (OH-, SD 5.85), 46.44 (OH+, SD 9.81), p = 0.021.	Balance was adjusted for age, sex, pain in lower limbs, ADL dependence

Supplementary table 2.3. (Continued)

First author	Physical functioning categories	Physical functioning data	Adjustments
		TUG time (s): 14.8 (OH-, SD 5.79), 17.08 (OH+, SD 7.94), p = 0.144.	MMSE score and insulin use
Gaxatte, 2017	Balance; gait; TUG; ADL	Instability when standing upright or absence of postural reaction upon sternal pressure (%): 70 (OH-), 74 (OH+), p = 0.29. Gait disorder according to Alexander and Goldberg classification (%): 86 (OH-), 87 (OH+), p = 0.87. TUG time > 20s (%): 58 (OH-), 64 (OH+), p = 0.20. Katz ADL score: 5.2 (OH-, SD 1.2), 4.9 (OH+, SD 1.4), p = 0.02.	-
Oishi, 2016	Balance; TUG	Self-reported symptoms of dizziness or loss of balance (%): 15.2 (OH-), 29.4 (OH+), p > 0.05. TUG time > 11s (%): 73.7 (OH-), 46.7 (OH+), p < 0.05.	-
Pasma, 2014	Balance	OR OH and balance impairment on semi-tandem stance test with eyes closed: 3.03, p < 0.03*.	OR OH and balance impairment was corrected for age and sex.
Press, 2015	ADL	Barthel index: vs 84.7 (OH-, SD 15.9), 82.9 (OH+, SD 16.5), p = 0.25.	-
Soysal a, 2014	Balance; gait; ADL	Tinetti balance score: 12.9 (OH-, SD 3.9), 11.9 (OH+, SD 3.7), p = 0.691. Tinetti gait score: 9.9 (OH-, SD 2.9), 9.8 (OH+, SD 3.1), p = 0.712. Basic ADL score (0-100 [worst-best]): 88.6 (OH-, SD 18.2), 84.6 (OH+, SD 21.0), p = 0.01.	-
Soysal b, 2016	Balance	Postural symptoms of dizziness, sweating and imbalance (%) 48.9 (OH-), 45.6 (OH+), p = 0.576.	-
Susman, 1989	ADL	Parkerson functional score: 27.5 (OH-), 26.0 (OH+) p > 0.05.	-
Geriatric inpatients			
Aries, 2012	ADL	No quantitative data reported. No association between OH and modified Rankin scale 3 months after stroke.	-
Bendini, 2007	ADL	Katz ADL score: 5.1 (whole population, SD 1.0; no values for OH- and OH+ group reported). Significant difference in ADL performance between OH- and OH+ group, p = 0.028.	Age and sex
Coutaz, 2012	ADL	Barthel index (day 1-3 after hospitalization): 72.1 (OH-, SD 18.3) 69.3 (OH+, SD 20.0), p = 0.303.	-
Jodaitis, 2015	ADL	OH and decline in Katz score over last month: OR 2.46 (CI 1.51-4.00).	Feeling of fainting, syncope and recurrent falls
Kihara, 1998	ADL	Barthel index: 17.8 (OH-, SD 6.6), 23.3 (OH+, SD 10.0), p < 0.05.	-
MacLennan, 1987	Mobility	Mobility grading (1-11 [worst-best]): 7.5 (no SBP drop, SD 3.8), 7.5 (drop < 20 mmHg, SD 3.7), 8.1 (SBP drop >20 mmHg, SD 3.6), p > 0.05.	-
Shen, 2015	Balance; gait; mobility; walking speed; HGS	Tinetti balance score: 13.7 (OH-, SD 1.48), 11.8 (OH+, SD 3.21), p = 0.003†. Gait disorder (%): 36.4 (OH-), 52.8 (OH+), p0.074. Use of walking aids (%): 10.0 (OH-), 19.4 (OH+), p = 0.119. Four-meter walk test (median in seconds): 6.5 (OH-, IQR 5.3-9.2), 6.0 (OH+, IQR 5.1-7.2), p 0.244. HGS (kg): 29.9 (OH-, SD 9.9), 27.9 (OH+, SD 9.0), p = 0.267.	Balance was adjusted for age
Siennicki-Lantz, 1999	ADL	Katz ADL index: Patients with Alzheimer dementia: 4.5 (OH-, range 1-7), 5.0 (OH+, range 3-6), p < 0.05. Elderly controls: 1 (OH-, range 1 - 1), 1 (OH+, range 1-2)	-
Vloet, 2005	Mobility	Self-reported mobility problems (%): 63.4 (OH-), 63.6 (OH+).	-
Nursing home residents			
Gray-Miceli a, 2012	Balance	Loss of balance (% of no. of falls): 56.0 (OH-), 62.5 (near OH), 50.0 (OH+), 27.6 (OH not measured), p = 0.004.	-
Gray-Miceli b, 2016	Balance; gait	Balance steady on initial standing (% of no. of falls): 43.4 (OH-), 22.2 (OH+), p = 0.09. Gait in steady line (% of no. of falls): 56.0 (OH-), 5.6 (OH+), p = 0.001.	-

Ooi, 1997	Mobility; ADL	Ambulation problem (%): 29.7 (OH-), 25.2 (Isolated OH), 26.7 (variable OH), 16.3 (persistent OH). p < 0.001. Arbitrary ADL score (higher scores indicating ADL independence): 1.7 (OH- SD 1.2), 1.6 (Isolated OH, SD1.4), 1.9 (variable OH, SD1.1), 1.8 (persistent OH, SD1.1). p = 0.60.	ADL was adjusted for age, sex, OH symptoms, BMI, medication, comorbidity and time of BP measurement
Patients with PD or parkinsonism			
Allcock, 2006	HY/UPDRS III	UPDRS III score (median): 17.0 (OH-, IQR 12.0), 19.0 (OH+, IQR 9.0), p = 0.08.	-
Ha, 2011	HY/UPDRS III	HY stage: Patients with PD: 2.39 (OH-, SD 0.86), 2.61 (OH+, SD 0.89), p = 0.01. Patients with atypical parkinsonism, without MSA: 2.90 (OH-, SD 1.07), 3.02 (OH+, SD 1.08), p = 0.77. Patients with MSA: 2.80 (OH-, SD 1.30), 3.50 (OH+, SD 1.26), p = 0.56.	-
Hohler, 2012	Balance; walking speed; TUG; ADL	Berg balance score: 29.58 (OH-, SD 13.01), 17.18 (OH+, SD 14.6), p = 0.019. Two-minute walk test (m): 30.0 (OH-, SD 10.8), 22.9 (OH+, SD 11.3), p = 0.044. TUG time (s): 42.9 (OH-, SD 28.9), 53.0 (OH+, SD 31.4), p = 0.304. Motor functional independence measure (self-care, sphincter control, transfers, locomotion; 13-91 [worst-best]): 30.0 (OH-, SD 10.82), 22.8 (OH+, SD 11.30), p = 0.044.	-
Matinolli, 2009	Mobility; walking speed; TUG; physical activity; UPDRS II; HY/UPDRS III	Use of walking aids (%): 31.8% (OH-), 39.7% (OH+), p = 0.734 Walking speed (m/s): 1.2 (OH-, SD 0.3), 1.2 (OH+, SD 0.4), p = 0.806 TUG time (s): 13.2 (OH-, SD 7.8), 13.0 (OH+, SD 7.0), p = 0.865 High leisure time physical activity according to Pfaffenbarger questionnaire (%): 57.9% (OH-), 49.2% (OH+), p = 0.734 UPDRS II score: 12.9 (OH-, SD 5.9), 14.1 (OH+, SD 6.3), p = 0.732 UPDRS III score: 25.2 (OH-, SD 11.9), 24.4 (OH+, SD 10.0), p = 0.804	-
Matsui, 2006	HY/UPDRS III	UPDRS III score: 36.3 (OH-, SD 16.7), 32.8 (OH+, SD 15.8), p > 0.05.	-
Merola, 2016	mobility; ADL; UPDRS II; HY/UPDRS III	Ambulatory capacity measure (sum of items 13, 14, 15, 29, 30 of the UPDRS): 3.90 (OH-, SD 0.62), 6.07 (OH+, SD 0.83), p = 0.035*. Katz ADL score: 5.68 (OH-, SD 0.45), 4.74 (OH+, SD 0.51), p = 0.029*. UPDRS II score: 10.19 (OH-, SD 6.91), 16.41 (OH+, SD 9.29), p = 0.041*. UPDRS III score: 28.17 (OH-, SD 12.15), 33.27 (OH+, SD 14.38), p = 0.284*.	Mobility, ADL and UPDRS II scores were adjusted for MOCA score and disease duration
Perez-Lloret, 2012	UPDRSII and HY/UPDRS III	Sum of UPDRS II and UPDRS III scores > 33 (%): 41 (OH-), 66 (OH+), p = 0.01. Adjusted OR = 2.21 (CI 0.81-6.07)	Age, polypharmacy, entacapone use, amantadine use, diuretics use
Sithinamsuwan, 2010	HY/UPDRS III	Frequency distribution of HY stage (%, 1 : 2 : 3 : 4 : 5) *OH-*: 36.7 : 28.6 : 28.6 : 4.1 : 2.0, *OH+*: 18.2 : 21.2 : 33.3 : 21.2 : 6.1, p = 0.003	-

OR: odds ratio; SD: standard deviation; CI: 95% confidence interval; MAP: mean arterial pressure; SBP: systolic blood pressure; LBNP: lower body negative pressure; MMSE: Mini Mental State Examination; MOCA: Montreal cognitive assessment; MSA: multiple system atrophy; NYHA: New York Heart Association classification of heart failure. *Data obtained by contacting authors. †Data extracted from figure.

Supplementary table S2.4. Outcome measures of studies included in and excluded from the meta-analyses, per physical functioning category

Physical functioning category	Outcome	Included studies	Excluded studies	Reason for exclusion
Balance performance	Tinetti balance score (C)	Aydin, 2017; Shen, 2015; Soysal a, 2014	-	
	Berg balance score (C)	Cordeiro, 2009; Hohler, 2012	-	
	Balance impairment on semi-tandem stance test with eyes closed (D)	Pasma, 2014	-	
	Instability when standing upright or absence of postural reaction upon sternal pressure (D)	Gaxatte, 2017	-	
	Self-reported postural symptoms (unsteadiness, dizziness) and loss of balance during standing (D)	Mader, 1987; Oishi, 2016; Rutan, 1992; Soysal b, 2016	Gray-Miceli a, 2012; Gray-Miceli b, 2016	Insufficient data reported
Gait characteristics	Tinetti gait score (C)	Aydin, 2017; Soysal a, 2014	-	
	Gait disorder according to Alexander and Goldberg classification (D)	Gaxatte, 2017	-	
	Gait disorder (not specified) (D)	Shen, 2015	-	
Mobility	Need of walking aid (D)	Matinolli, 2009; Shen, 2015; Zhu, 2016	-	
	Mobility score assessing need of walking aids and help of other persons (C)	MacLennan, 1987	-	
	Ambulatory capacity measure (sum of items 13, 14, 15, 29, 30 of the UPDRS) (C)	Merola, 2016	-	
	Self-reported difficulty walking or mobility problems (D)	Ooi, 1997; Rutan, 1992; Vloet, 2005	-	
Walking speed	6-minute walk test (C)	Kobayashi, 2012	-	
	2-minute walk test (C)	Hohler, 2012	-	
	4-meter walk test (C)	Shen, 2015	-	
	Walking speed (duration/distance not specified) (C)	Matinolli, 2009	-	
	Height normalized walking speed (duration/distance not specified) (C)	Romero-Ortuno, 2011	-	
	10-foot walk test (C)	-	Masaki, 1998	Insufficient data reported
TUG	Timed Up and Go time (C)	Cordeiro, 2009; Hohler, 2012; Matinolli, 2009; Matsubayashi, 2017	-	
	Timed Up and Go time > 20s (D)	Gaxatte, 2017	-	
	Timed Up and Go time > 11s (D)	Oishi, 2016	-	
HGS	Hand grip strength (C)	Kobayashi, 2012; Romero-Ortuno, 2011; Shen, 2015	Masaki, 1998	Insufficient data reported
Physical frailty	Fried frailty criteria (D)	Rockwood, 2012; Romero-Ortuno, 2011	-	
Exercise tolerance	MAP as response to LBNP in group with high exercise tolerance (peak O_2 uptake > 30ml/min/kg) compared to group with low exercise tolerance (peak O_2 uptake 18-28 ml/min/kg) (C)	-	Formes, 2010	Insufficient data reported
	Peak O_2 consumption on graded max leg exercise test (C)	-	Tang, 2012	Only study in this category
	Prevalence of OH in subjects with NYHA class III or IV compared to subjects with NYHA class 1 (D)	-	Tilvis, 1996	Insufficient data reported
Physical activity	Physical activity (time spent outdoor walking above/below 20th percentile of investigated population) (D)	Romero-Ortuno, 2011	-	
	Physical activity during leisure (not specified) (D)	Zhu, 2016	-	

Supplementary table S2.4. (Continued)

Physical functioning category	Outcome	Included studies	Excluded studies	Reason for exclusion
	Physical activity during leisure (Pfaffenbarger questionnaire) (D)	Matinolli, 2009	-	
ADL performance	Barthel index (C)	Coutaz, 2012; Kihara, 1998; Press, 2015	-	
	Katz ADL score (C)	Gaxatte, 2017; Merola, 2016	Bendini, 2007; Siennicki-Lantz, 1999	Insufficient data reported
	ADL scale assessing walking, climbing stairs, preparing meals, doing housework, shopping (D)	Ensrud, 1992	-	
	ADL scale assessing walking, climbing stairs, eating, dressing, toileting, bathing, grooming and taking medicine (C)	Matsubayashi, 2017	-	
	ADL scale assessing transfers, locomotion, self-care and sphincter control (C)	Hohler, 2012	-	
	Basic activities of daily living (not specified) (C)	Aydin, 2017; Soysal a, 2014	-	
	Self-reported ADL problems (not specified) (D)	Rutan, 1992	-	
	Modified Rankin Scale (C)	-	Aries, 2012	Insufficient data reported
	Parkerson functional score (C)	-	Susman, 1989	Insufficient data reported
	Decline in Katz score over last month (C)	-	Jodaitis, 2015	Only study with longitudinal design
UPDRS II ADL performance	UPDRS II score (C)	Matinolli, 2009; Merola, 2016	-	
HY/UPDRS III performance	HY score (C)	Ha, 2011; Sithinamsuwan, 2010	-	
	UPDRS III score (C)	Allcock, 2006; Matinolli, 2009; Matsui, 2006; Merola, 2016	-	
Outcomes not classifiable into one physical functioning category				
Balance performance, mobility and walking speed	Postural-locomotor-manual test (C)	-	Guo, 2003	Outcome not classifiable into one category of physical functioning
UPDRS II ADL performance and HY/UPDRS III performance	Sum of UPDRS II and UPDRS III scores (C)	-	Perez-Lloret, 2012	Outcome not classifiable into one category of physical functioning

TUG: Timed Up and Go time; HGS: handgrip strength; ADL: activities of daily living; UPDRS: Unified Parkinson's Disease Rating Scale; HY: Hoehn and Yahr Scale; MAP: mean arterial pressure; LBNP: lower body negative pressure; NYHA: New York Heart Association classification of heart failure; C: continuous outcome; D: dichotomous outcome.

Chapter 3

Orthostatic hypotension and falls in older adults: a systematic review and meta-analysis

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Abstract

Objectives: Orthostatic hypotension is a potential risk factor for falls in older adults, but existing evidence on this relationship is inconclusive. This study addresses the association between orthostatic hypotension and falls.

Design: Systematic review and meta-analysis of the cross-sectional and longitudinal studies assessing the association between orthostatic hypotension and falls, as preregistered in the PROSPERO database (CRD42017060134).

Setting and Participants: A literature search was performed on February 20th 2017 in MEDLINE (from 1946), PubMed (from 1966) and EMBASE (from 1947) using the terms "orthostatic hypotension", "postural hypotension" and "falls". References of included studies were screened for other eligible studies. Study selection was performed independently by two reviewers using the following inclusion criteria: published in English; mean/median age of the population ≥ 65 years; blood pressure measurement before and after postural change; assessment of the association of orthostatic hypotension with falls. The following studies were excluded: conference abstracts, case reports, reviews and editorials. Data extraction was performed independently by two reviewers.

Measures: Unadjusted odds ratios of the association between orthostatic hypotension and falls were used for pooling using a random-effects model. Studies were rated as high, moderate or low quality using the Newcastle Ottawa Scale.

Results: Out of 5646 studies, 63 studies (51,800 individuals) were included in the systematic review and 50 studies (49,164 individuals) in the meta-analysis. Out of 63 studies, 39 were cross-sectional and 24 were longitudinal. Orthostatic hypotension was positively associated with falls (odds ratio 1.73, 95% confidence interval 1.50-1.99). The result was independent of study population, study design, study quality, orthostatic hypotension definition and blood pressure measurement method.

Conclusions and Implications: Orthostatic hypotension is significantly positively associated with falls in older adults, underpinning the clinical relevance to test for an orthostatic blood pressure drop and highlighting the need investigate orthostatic hypotension treatment to potentially reduce falls.

Introduction

Orthostatic hypotension (OH) is defined as a blood pressure drop of at least 20 mmHg in systolic blood pressure (SBP) and/or 10 mmHg in diastolic blood pressure (DBP) within three minutes after standing up.[1] OH is prevalent at older age and in individuals with comorbidities such as cardiovascular disease[2] and Parkinson's disease (PD)[3] as this disease often entails dysfunction of the autonomous nervous system.

OH is considered a risk factor for falls, potentially causing falls directly (i.e. within

seconds) after standing up by decreased brain perfusion and subsequent decreased brain oxygenation.[4] Alternatively, OH might cause falls by indirect mechanisms, such as cerebral white matter lesions.[5] However, studies on the association of OH and falls are inconclusive as some report a positive association[6,7] and others found no association.[8,9] Previous studies summarized existing evidence on the association of OH and falls, but either did not perform a meta-analysis[10–12] or were restricted to prospective studies with available individual patient data, resulting in a low number of included studies, preventing subgroup analysis for e.g. study population.[13]

The aim of this study was to systematically review the existing literature and perform a meta-analysis on the association between OH and falls in various populations of older adults aged 65 years or older and to address the influence of study population, study design (i.e. cross sectional or longitudinal), study quality, applied OH definition and blood pressure measurement method. It was hypothesized that OH is positively associated with falls.

Methods

The review protocol was registered at the PROSPERO International prospective register of systematic review (CRD42017060134). This study was performed in accordance with the PRISMA and MOOSE guidelines. A search was performed in MEDLINE (from, 1946), Pubmed (from 1966), and EMBASE (from 1947) to 20th of February 2017 and included the terms “orthostatic hypotension”, “postural hypotension”, and “falls”. The complete search strategy is presented in supplementary file S2.1.

Study selection

Screening of titles and abstracts and subsequent full text articles was performed independently by two reviewers (AM and PTSBH). Any disagreements between reviewers were resolved by a third reviewer (EMR, CGM or ABM). Studies were eligible if they met the following inclusion criteria: published in English; mean or median age of the included population 65 years or older; blood pressure measurements before and after a postural change; assessment of falls; assessment of the association of OH with falls. Conference abstracts, case reports, reviews, editorials and letters to the editor were excluded as these publications do not report original data or do not allow for study quality assessment. Studies were organized and managed using EndNote (Version: X8.2. Clarivate Analytics, Philadelphia, USA). References of eligible studies were screened for other studies meeting the criteria.

Data extraction and study quality assessment

The following variables were independently extracted by two reviewers (AM and PTSBH): first author; year of publication; age; sex; study population; study

design; type of postural change (e.g. active stand or head up tilt); blood pressure measurement method (i.e. intermittent or continuous); OH definition; prevalence of OH; odds ratio (OR) of the association of OH and falls, or fall prevalence in the group with and without OH.

The quality of the included studies was assessed independently by two authors (AM and PTSBH) using the nine-point Newcastle-Ottawa Scale (NOS), higher scores indicating lower risk of bias. Studies with NOS scores ranging from 0-3, 4-6 and 7-9 points were considered as low, moderate and high quality, respectively. The specified NOS for this study is provided in supplementary file S3.1.

Study selection for meta-analysis and data synthesis

Studies were included in the meta-analysis if an OR was reported or an OR could be reconstructed from reported data on fall prevalence in the group with and without OH. Unadjusted ORs were used rather than adjusted ORs to reduce heterogeneity. If available, continuously measured blood pressure was used rather than intermittently measured blood pressure as continuous blood pressure measurements are more sensitive for the diagnosis of OH.[14] The consensus definition of OH (i.e. SBP drop ≥ 20 mmHg or DBP drop ≥ 10 mm Hg within 3 minutes after standing up) was used rather than the systolic OH definition (i.e. SBP drop ≥ 20 mmHg within 3 minutes after standing up) and the initial OH definition (iOH, i.e. SBP drop ≥ 40 mmHg or DBP drop ≥ 20 mm Hg within 15 seconds after standing up). Results of active stand tests rather than other types of postural change (e.g. head up tilt test) were used, as these most resemble daily life situations.

Meta-analysis

Meta-analyses of studies with an available reported or calculated OR were performed using Review Manager (RevMan. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A random effects model was used as the included studies differed with respect to study population and design. Subgroup analyses were performed for study population (categorized as community-dwelling adults, geriatric outpatients, geriatric inpatients, nursing home residents, patients with PD and patients with other specific diseases), study design (i.e. cross-sectional or longitudinal), study quality (assessed using the NOS), OH definition (i.e. consensus OH, systolic OH, iOH or other OH definition), and blood pressure measurement method (continuous or intermittent), if at least two studies were available. Heterogeneity was investigated using the I^2 statistic, values <25%, 25-50% and >50% indicating low, moderate and high heterogeneity, respectively. P-values < 0.05 were considered statistically significant. Risk for publication bias was calculated using Egger's test for meta-analyses including at least ten studies using a significance level of 10%.[15]

Results

Study selection

Figure 3.1 shows the PRISMA flow diagram of study identification and selection. Out of 8133 abstracts, 5645 were unique. Of these, 332 were selected for full-text screening, 63 studies were included in the systematic review. Fifty studies reported an OR or prevalence data, enabling inclusion in the meta-analysis.

Systematic review

Table 3.1 lists the study characteristics, results on the association between OH and falls and study quality of all 63 studies (51,800 individuals). Study populations consisted of community-dwelling adults (17 studies), geriatric outpatients (12 studies), geriatric inpatients (5 studies), nursing home residents (14 studies), patients with PD (8 studies) and patients with specific other diseases (7 studies). Thirty-nine studies were cross-sectional and 24 studies were longitudinal. Seven studies

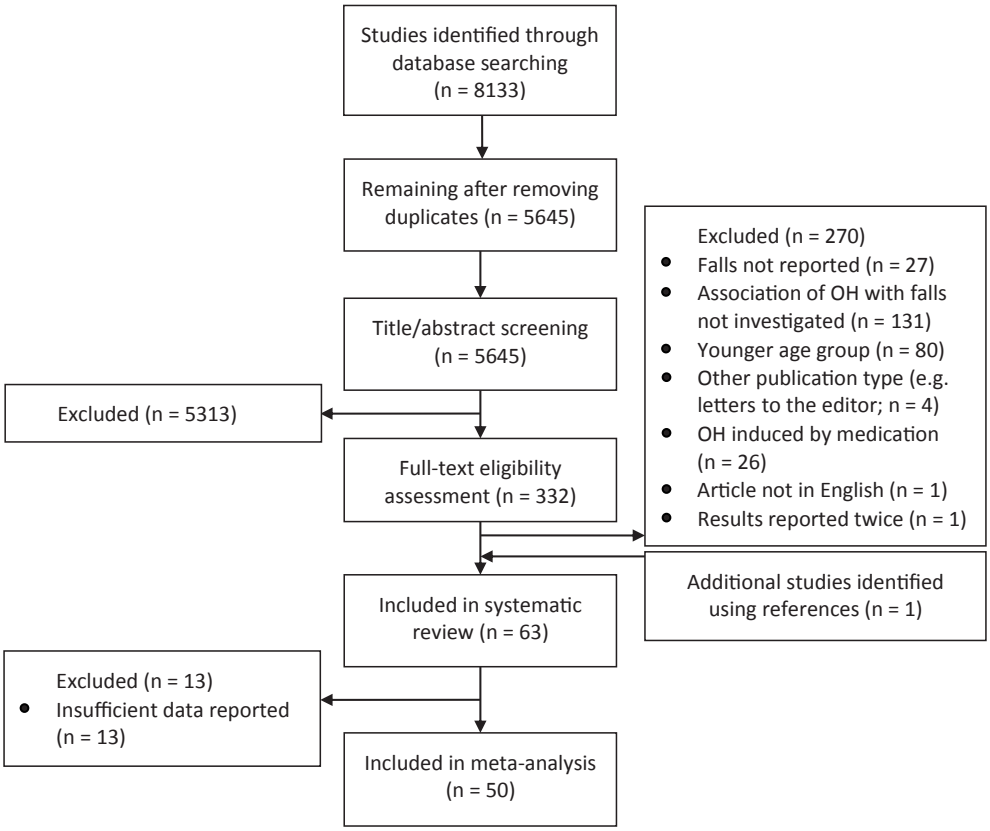

Figure 3.1. PRISMA flow diagram of study identification and selection

Table 3.1. Study characteristics, the reported association of OH with falls (positive, negative or absent) and study quality of the included studies

First author, year of publication	N	Age, years #	Female, %	Study design	OH definition	Postural change	BP measurement	Assessment of falls	Period of fall assessment, m	OH, %	Association, +/=/-	NOS	Meta-analysis, +/-
Community-dwelling adults													
Campbell, 1989[16]	761	>70	59.9	L	sOH	AS	I	D	12	31.4	=	5	+
Chang, 2010[17]	1361	72 (5.1)	39.6	Cs	cOH	AS	NR	I/Q	12	30.9	=	5	+
Ensrud, 1992[18]	9704	72 (65-99)	100	Cs	sOH	AS	I	I/Q	12	14.0	=	3	+
Gangavati, 2011[19]	722	78 (5.1)	73.1	L	cOH	AS	I	D	12	6.0	=	7	+
Heitterachi, 2002[20]	70	77 (5.9)	80	L	sOH	HUT	C	I/Q	12	14	+	6	-
Kario, 2001[21]	266	76 (5.0)	46.0	L	sOH -	AS	I	D	12	19.5	=	4	-
Liu, 1995[22]	96	83 (6.0)	82	L	sOH	AS	I	D	12	NR	=	5	-
Lord, 1995[23]	414	74 (6.3)	100	L	sOH	AS	I	I/Q	12	22.6	=	4	-
Mader, 1987[24]	300	70 (56-93)	77.0	Cs	sOH	AS	I	I/Q	12	10.7	=	3	+
McDonald, 2016[25]	79	73 (6.8)	51	L	cOH	AS	C	D	12	81	+	7	+
Menant, 2016[26]	529	80 (4.4)	52.2	L	cOH	HUT	I	D	12	22.1	+	7	+
Romero-Ortuno, 2011[27]	442	72	72.0	Cs	cOH	AS	C	I/Q	6	94.1	=	5	+
Rutan, 1992[28]	4931	> 65	56.5	Cs	cOH	AS	I	I/Q	12	16.2	+	5	+
Wong, 2013[29]	520	80 (4.4)	50.8	L	cOH	HUT	I	D	12	22.7	=	6	+
Yu, 2009[30]	1512	71 (6.5)	59.1	Cs	NR	NR	NR	I/Q, MR	NR	21.9	+	2	+
Zhu, 2016[31]	364	75 (64-98)	50.5	Cs	cOH	AS	I	I/Q	12	11.0	=	3	+
Zia, 2015[32]	358	74 (6.5)	67.6	Cs	cOH	AS	I	I/Q	12	22.3	+	5	+
Geriatric outpatients													
Allan, 2009[33]	179	76 (6.2)	40.8	L	cOH	AS	C	D	12	12.5	+	8	-
Aydin, 2017[34]	290	75 (8.7)	59.3	Cs	cOH	AS	I	I/Q	12	37.2	=	4	+
Blumenthal, 1980[35]	100	60-95	70.0	Cs	sOH +	AS	I	I/Q	NR	39.0	+	1	-
Davies, 2001[36]	80	78 (7.3)	20	Cs	sOH	AS	C	I/Q	NR	23	=	5	+
Gaxatte, 2017[7]	833	80 (7.4)	73.1	L	cOH	AS	I	I/Q	6	23.9	+	5	+
Miu, 1997[37]	400	74	58.8	Cs	sOH	AS	I	I/Q	12	22.8	=	2	+
Pasma, 2014[14]	58	81 (7.0)	57	Cs	iOH/ cOH	As	C	I/Q	12	57	+	5	+
Press, 2016[9]	571	84 (6.1)	64.1	Cs	cOH	AS	I	I/Q	12	32.2	=	3	+
Saedon, 2016[38]	267	74 (6.6)	68.8	Cs	cOH	AS	C	I/Q	12	69.7	+	5	+
Susman, 1989[39]	100	73 (65-90)	62.0	Cs	sOH	AS	I	I/Q	12	31.0	=	3	+
Van der Velde, 2007a[40]	217	77 (5.8)	65.6	Cs	cOH	HUT	C	I/Q	12	59.8	+	4	+
Van der Velde, 2007b[41]	211	77 (5.7)	65.3	Cs	cOH	HUT	C	I/Q	12	60.1	+	8	+
Geriatric inpatients													
Chen, 2009[42]	404	68 (16.9)	26.2	L	cOH	NR	I	I/Q	LoS	4.2	+	4	+

Coutaz, 2012[43]	340	81 (8.1)	68.5	L	cOH	AS	I	I/Q	6	51.5	=	4	+
Jodaitis, 2015[44]	285	85 (5.0)	54.0	Cs	cOH	AS	I	I/Q	6	41.0	+	4	+
Passant, 1997[45]	151	75	38.6	L	sOH	AS	I	NR	NR	46.0	=	3	+
Soysal, 2016[46]	407	75 (8.5)	62.9	Cs	cOH	HUT	I	I/Q	12	22.1	+	4	+
Nursing home residents													
Bumin, 2002[47]	33	70 (2.2)	NR	Cs	sOH	StS	I	I/Q	NR	30	=	2	+
Graafmans, 1996[48]	354	83 (6.0)	85.0	L	cOH	AS	NR	D	4	21.0	=	6	+
Gray-Miceli, 2016[49]	47	91 (5.8)	74	Cs	cOH	NR	NR	MR	NR	15	=	3	-
Hall, 2015[50]	510	77 (11.5)	26.9	Cs	sOH	NR	NR	I/Q	6	8.6	=	3	-
Hartog, 2015[51]	290	81 (9.9)	71.0	Cs	cOH	AS	I	I/Q	12	36.6	=	4	+
Hartog, 2017[8]	246	82 (76-87)	70.0	L	cOH	AS	I	Obs	15.6	37.0	=	7	-
Jonsson, 1990[52]	58	86 (5.7)	66	Cs	sOH	AS	C	MR	6	26	=	2	+
Makhlouf, 2000[53]	165	73 (7.6)	62.4	Cs	cOH	StS	I	I/Q	12	14.0	=	3	+
Maurer, 2004[54]	111	88 (7.0)	82.0	L	cOH	StS	C	MR	9	NR	=	5	-
Maurer, 2005[55]	139	88 (7.0)	85.0	L	NR	StS	C	MR	10	34.0	=	4	-
Ooi, 1997[56]	911	79 (12.1)	80.0	Cs	cOH	AS	I	I/Q	6	51.5	=	4	+
Ooi, 2000[57]	844	> 60	81.7	L	cOH	AS	I	Obs	14.4	53.9	+	7	+**
Shaw, 2015[58]	46	83 (7.8)	54	Cs	cOH	AS	C	I/Q	12	35	=	4	+
Tinetti, 1986[59]	79	79 (7.0)	68	L	sOH	AS	NR	Obs	3	4	=	4	-
Patients with Parkinson's disease													
François, 2017[6]	17702	74 (11.0)	59.1	Cs	NR	NR	NR	MR	12	20.1	+	2	+
Gray, 2000[60]	118	> 40	38.0	L	cOH	NR	NR	D	3	16.4	=	4	+
Kerr, 2010[61]	101	66 (8.2)	32.7	L	NR	NR	NR	D	6	18.1	+	3	+
Koller, 1989[62]	100	67	39.0	Cs	sOH	NR	NR	I/Q	12	5.9	=	2	+
Matinolli, 2009[63]	120	68 (10.1)	33.3	Cs	cOH	AS	I	I/Q	1	52.5	=	4	+
Merola, 2016[64]	121	66 (9.4)	43.0	Cs	cOH	HUT	I	I/Q	6	30.6	+	4	+
Rascol, 2015[65]	672	> 67	42.1	Cs	NR	NR	NR	I/Q	1	12.5	+	2	+
Sithinamsuwan, 2010[66]	82	69 (10.3)	70	Cs	cOH	AS	I	MR	NR	40	=	4	+
Patients with specific other diseases													
Azidah, 2012[67, *]	288	> 60	54.2	Cs	cOH	AS	NR	I/Q	12	12.2	+	3	+
Galizia, 2013[68, †]	90	76 (8.0)	88	Cs	cOH	AS	I	I/Q	6	47	+	3	+
Joo, 2002[69, ‡]	104	77 (5.4)	69.2	L	sOH	AS	NR	I/Q	5	23.5	=	5	-
Kadir, 2011[70, *]	131	68 (5.6)	0	Cs	NR	NR	NR	I/Q	12	NR	+	3	+
Shen, 2015[71, §]	176	77 (6.6)	42.6	Cs	cOH	AS	I	I/Q	12	20.5	=	6	+
Van Hateren, 2012[72, *]	563	75 (72-79)	52.9	Cs	cOH	AS	I	I/Q	12	24.3	=	4	+
Van Helden, 2007[73, ‖]	277	67 (50-91)	72.0	L	cOH	AS	I	I/Q	3	12.0	=	5	+

NR: not reported; L: longitudinal; Cs: cross-sectional; cOH: OH according to consensus definition; sOH: systolic OH; sOH-: sOH without symptoms; sOH+: sOH with symptoms; iOH: initial OH; AS: active stand; BP: blood pressure; HUT: head up tilt; StS: sit to stand; I: intermittent: C: continuous; I/Q: interview or questionnaire; D: fall diary; MR: falls assessed by screening medical record; Obs: falls assessed by observation; LoS: fall assessment period as long as the length of stay in hospital or nursing home; NOS: study quality on the Newcastle Ottawa Scale. * Patients with type II diabetes. † Patients with degenerative joint disease. ‡ Patients with depressive disorder. § Patients with hypertension. ‖ Patients with a fracture; #Age is presented as a mean (standard deviation), median (range), or range. ** In the meta-analyses and subgroup analyses, this study was analyzed as cross sectional as insufficient longitudinal data were available for meta-analysis.

were of high quality, 35 studies of moderate quality and 21 studies of low quality. Supplementary table S3.2 lists the study quality per NOS item. Thirty-eight studies applied the consensus definition of OH, 16 studies used the systolic OH definition and 9 studies used other definitions or did not report the used definition. The used blood pressure measurement method was intermittent in 36 studies, continuous in 13 studies and not reported in 14 studies. Twenty-four out of the 63 studies reported a positive association of OH and falls and the other studies reported no association.

Meta-analysis

Figure 3.2 shows the forest plot of the 50 studies included in the meta-analysis (49,164 individuals). OH was significantly positively associated with falls (OR 1.73; 95% confidence interval (CI) 1.50-1.99; p <0.001). Overall heterogeneity was high (I^2 = 68%). Egger's test showed no evidence for publication bias (p = 0.431).

Figure 3.3 shows the subgroup analyses for study population, study design, study quality, OH definition and blood pressure measurement method. Significant positive associations were found in all subgroups. The OR of the association between OH and falls was highest for patients with PD (OR 2.30; 95% CI 1.53-3.48), longitudinal studies (OR 2.05; 95% CI 1.49-2.80), studies with low quality (OR 1.77; 95% CI 1.36-2.32), studies using the systolic OH definition (OR 1.69; 95% CI 1.02-2.81) and studies using continuous blood pressure measurements (OR 2.35; 95% CI 1.76-3.13) in these respective subgroup analyses. Heterogeneity in all subgroups was moderate or high, except for studies using the continuous blood pressure measurements, which had low heterogeneity.

Discussion

This systematic review and meta-analysis demonstrated a consistent positive association between OH and falls. This is the first study showing independence of this association from study population, study design, study quality, OH definition and blood pressure measurement method. These results indicate the clinical importance to test for OH in older adults and the need to study if OH interventions reduce falls.

The found positive association between OH and falls was independent of study quality, which together with the large number of included individuals supports the robustness of the evidence. Furthermore, Egger's test did not indicate the presence of publication bias.

The association of OH with falls in cross-sectional studies might indicate a potential causal relationship, which could work in both directions. OH might cause an acute drop in cerebral oxygenation due to an impaired cerebral autoregulation, resulting in dizziness and falls.[4] Alternatively, OH might cause brain atrophy, microbleeds and white matter brain lesions, resulting in falls.[5] OH might also cause falls through impaired muscle microcirculation as one study found an association

Study	OH, n		OR (95% CI)
	Yes	No	
Aydin, 2017	182	108	0.98 [0.55, 1.75]
Azidah, 2012	253	35	3.06 [1.42, 6.55]
Bumin, 2012	23	10	3.63 [0.74, 17.85]
Campbell, 1989	427	334	3.40 [2.44, 4.75]
Chang, 2010	940	421	1.30 [0.97, 1.75]
Chen, 2009	387	17	4.94 [1.40, 17.46]
Coutaz, 2012	196	144	1.29 [0.83, 1.99]
Davies, 2001	62	18	1.33 [0.42, 4.24]
Ensrud, 1992	8345	1359	1.02 [0.91, 1.15]
Francois, 2017	17421	281	1.39 [1.06, 1.83]
Galizia, 2013	48	42	4.30 [1.39, 13.28]
Gangavati, 2011	663	59	1.46 [0.83, 2.58]
Gaxatte, 2017	417	120	1.80 [1.19, 2.71]
Graafmans, 1996	280	74	2.85 [1.69, 4.82]
Gray, 2000	97	19	2.96 [0.91, 9.57]
Hartog, 2015	184	106	0.95 [0.52, 1.73]
Jodaitis, 2015	168	117	2.46 [1.51, 4.00]
Jonsson, 1990	46	12	1.07 [0.28, 4.09]
Kadir, 2011	93	38	3.37 [1.04, 10.93]
Kerr, 2010	92	8	7.57 [1.11, 51.83]
Koller, 1989	96	4	5.23 [0.55, 49.36]
Mader, 1987	265	32	0.52 [0.19, 1.40]
Makhlouf, 2000	142	23	2.11 [0.61, 7.27]
Matinolli, 2009	57	63	1.68 [0.78, 3.63]
McDonald, 2016	61	18	4.89 [1.57, 15.24]
Menant, 2016	412	117	1.02 [0.67, 1.53]
Merola, 2016	84	37	4.74 [2.00, 11.23]
Miu, 1997	309	91	1.41 [0.74, 2.69]
Ooi, 1997	442	469	1.10 [0.82, 1.47]
Ooi, 2000	420	424	1.22 [0.89, 1.66]
Pasma, 2014	51	7	2.45 [0.75, 8.03]
Passant, 1997	80	71	2.72 [1.37, 5.42]
Press, 2016	368	172	0.98 [0.61, 1.58]
Rascol, 2015	588	84	2.77 [1.65, 4.64]
Romero-Ortuno, 2011	26	416	1.87 [0.43, 8.13]
Rutan, 1992	4015	893	1.73 [1.19, 2.51]
Saedon, 2016	81	186	2.89 [1.56, 5.35]
Shaw, 2015	31	16	1.46 [0.42, 5.04]
Shen, 2015	140	36	1.62 [0.73, 3.59]
Sithinamsuwan, 2010	49	33	1.50 [0.55, 4.09]
Soysal, 2016	317	90	2.34 [1.44, 3.79]
Susman, 1989	69	31	2.14 [0.65, 7.01]
Van der Velde, 2007a	87	130	2.54 [1.37, 4.71]
Van der Velde, 2007b	84	127	2.30 [1.29, 4.09]
Van Hateren, 2012	426	137	0.94 [0.61, 1.45]
Van Helden, 2007	244	33	1.98 [0.82, 4.76]
Wong, 2013	402	118	1.06 [0.70, 1.60]
Yu, 2009	1181	331	1.92 [1.12, 3.29]
Zhu, 2016	324	40	1.74 [0.80, 3.78]
Zia, 2015	278	80	1.58 [0.95, 2.64]
Total	**41533**	**7631**	**1.73 [1.50, 1.99]**
P < 0.00001			
I^2 = 68%			

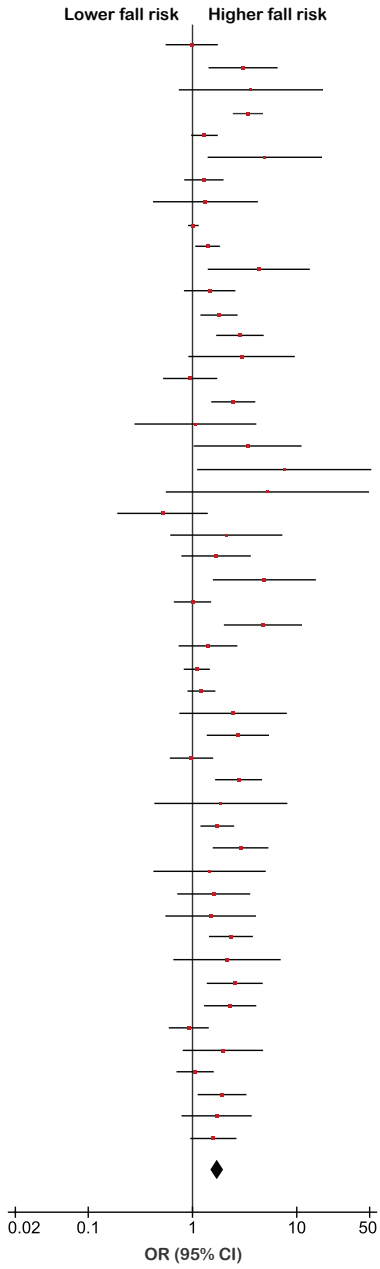

Figure 3.2. Forest plot of the meta-analysis of the association between OH and falls. OR: odds ratio; CI: confidence interval

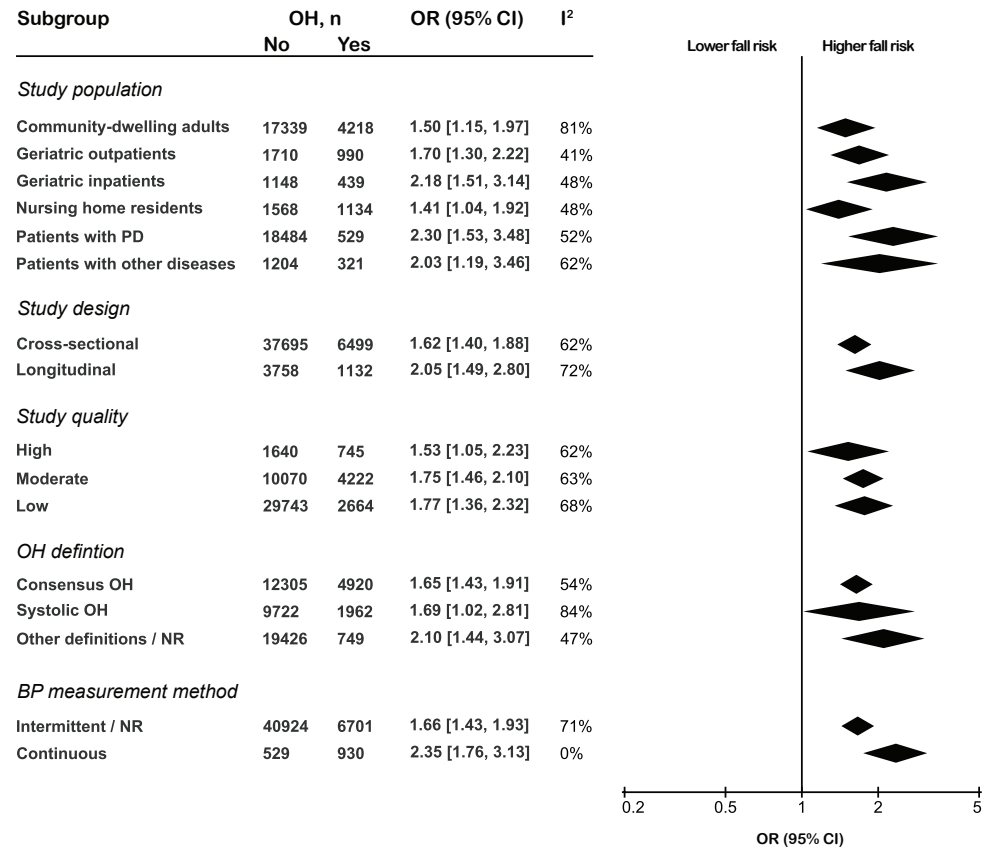

Figure 3.3. Forest plot of the subgroup analyses of the association between OH and falls for study population, study design, study quality, OH definition and blood pressure measurement method. PD: Parkinson's disease; NR: not reported; OR: odds ratio; CI: confidence interval

of OH with muscle ischemia.[74] Conversely, falls might cause OH by fear of falls, consequent behavioral changes including lower physical activity, resulting in deconditioning and muscle loss.[75] However, current evidence does not support this, as OH was not found to be associated with physical activity.[27,31,63] Furthermore, the association of OH with falls in longitudinal studies, which tested for OH at baseline and assessed falls during follow up, suggests OH being the cause rather than consequence of falls. In patients with OH, a common neural degenerative process might underlie the association between OH and falls, as PD both affects the autonomic system, causing OH, and the dopaminergic neurons in the nigrostriatal system, causing postural instability.[76,77]

In the subgroup analysis for blood pressure measurement method, the association between OH and falls was strongest in the subgroup of studies using

continuous blood pressure measurements, suggesting that testing OH using this method has largest clinical relevance. This is in line with a previous study, which reported that OH and iOH assessed using beat-to-beat continuous blood pressure measurement had a higher sensitivity and association with balance performance than OH assessed using intermittent blood pressure measurements 1 and 3 minutes after postural change.[14] These findings suggest that continuous blood pressure measurements might potentially be useful to identify patients with OH, in whom balance performance responds positively to OH treatment, advocating the use of continuous blood pressure measurements in clinical practice.

The evidence for OH treatment efficacy to prevent falls is circumstantial as no clinical trial assessing the effect of OH treatment on falls is available. Two randomized controlled trials demonstrated an improvement of OH symptoms in patients with neurogenic OH and patients with PD after treatment with midodrine and droxidopa, respectively.[78,79] Two cohort studies found an improvement of gross motor and balance function and symptoms in patients with PD.[80,81] These studies and the results of the present study suggest OH treatment may be effective to reduce falls, but future studies are needed to address this issue.

Clinical implications

The results highlight the clinical relevance of blood pressure measurements before and after postural change in a variety of populations of older adults and indicate OH as a potential predictor of falls. It should be tested if OH treatment is beneficial to reduce falls.

Strengths and limitations

The main strength of this review was the large number of included studies and diverse populations of individuals. These large numbers enabled subgroup analyses for study population, study design, study quality, OH definition and blood pressure measurement method. However, adjustment for potential confounders was limited, as insufficient studies adjusted for age, sex and other potential confounders to perform separate meta-analyses. Furthermore, most studies were of moderate or low quality and no conclusions can be drawn about any causal relationship between OH and falls.

Conclusion

OH was positively associated with falls in older adults, independent of study population, study design, study quality, OH definition and blood pressure measurement method. These results underpin the clinical importance of orthostatic blood pressure measurements in older adults and suggest the use of continuous blood pressure monitors. Furthermore, the association between OH and falls highlights the need to investigate if OH treatment reduces falls.

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Supplementary material

Suppemantary file S3.1. Specified NOS scale

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1. Representativeness of the exposed cohort with orthostatic hypotension
    a. Subjects representative of the average subjected aged 65 years and older with orthostatic hypotension *
    b. Not representative or no description
2. Selection of the non-exposed cohorts: subjects without orthostatic hypotension from the same community
    a. Yes *
    b. No
    c. No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure: how is orthostatic hypotension diagnosis made
    a. Blood pressure measured both continuously and intermittently *
    b. Blood pressure was measured continuously *
    c. Blood pressure measured intermittently
    d. No description or unclear
4. How was orthostatic hypotension defined?
    a. Based on widely accepted definition of OH *
    b. Other
    c. Not specified

Comparability

5. Adjustment for age and sex
    a. The study adjusts for: age or sex*
    b. The study does not adjust for age or sex
6. Adjustment for other confounders
    c. The study adjusts for other factors; medication (e.g. antihypertensives, ACE inhibitors, beta blockers), co-morbidities (e.g. Parkinson) etc.*
    d. The study does not adjust for other factors

Outcome

7. Assessment of falls outcome
    a. Observed by physician or self-reported prospective *
    b. Self-reported retrospective
    c. No description
    d. Other
8. Was follow-up long enough for fall outcomes to occur
    e. Yes, > 6 months *
    f. No, < 6 months
    g. No follow up in article
9. Adequacy of follow-up of cohorts
    h. Complete follow up- all subjects accounted for *
    i. Subjects lost to follow up unlikely to introduce bias- number lost is less than or equal to 20% or description of those lost suggested no different from those followed *
    j. Follow up rate less than 80% and on description of those lost
    k. Not described or not applicable

*= one point

Supplementary table S3.2 NOS score per study

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Score
Community-dwelling adults										
Campbell, 1989	*	*					*	*	*	5
Chang, 2010	*	*		*	*	*				5
Ensrud, 1992	*	*			*					3
Gangavati, 2011	*	*			*	*	*	*	*	7
Heitterachi, 2002	*	*	*				*	*	*	6
Kario, 2001	*						*	*	*	4
Liu, 1995	*			*			*	*	*	5
Lord, 1995	*						*	*	*	4
Mader, 1987	*	*					*			3
McDonald, 2016	*	*	*	*			*	*	*	7
Menant, 2016	*	*		*	*		*	*	*	7
Romero-Ortuno, 2011	*	*	*	*			*			5
Rutan, 1992	*	*		*	*	*				5
Wong, 2013	*	*		*			*	*	*	6

Supplementary table S3.2 (Continued)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Score
Yu, 2009	*	*								2
Zhu, 2016	*	*		*						3
Zia, 2015	*	*		*	*	*				5
Geriatric outpatients										
Allan, 2009	*	*	*		*	*	*	*	*	8
Aydin, 2017	*	*		*			*			4
Blumenthal, 1980	*									1
Davies, 2001	*	*	*				*		*	5
Gaxatte, 2017	*	*		*			*	*		5
Miu, 1997	*	*								2
Pasma, 2014	*		*	*	*		*			5
Press, 2016	*	*		*						3
Saedon, 2016	*	*	*	*	*	*				6
Susman, 1989	*	*		*						3
Van der Velde, 2007a	*	*	*	*						4
Van der Velde, 2007b	*	*	*	*	*	*	*		*	8
Geriatric inpatients										
Chen, 2009	*	*		*			*			4
Coutaz, 2012	*	*		*			*			4
Jodaitis, 2015	*	*		*		*				4
Passant, 1997	*	*				*				3
Soysal, 2016	*	*		*			*			4
Nursing home residents										
Bumin, 2002	*	*								2
Graafmans, 1996	*	*		*	*		*	*		6
Gray-Miceli, 2016	*	*		*						3
Hall, 2015	*				*	*				3
Hartog, 2015	*			*	*	*				4
Hartog, 2017	*			*	*	*	*	*	*	7
Jonsson, 1990	*		*							2
Makhlouf, 2000	*	*		*						3
Maurer, 2004	*		*				*	*	*	5
Maurer, 2005	*		*					*	*	4
Ooi, 1997	*	*		*		*				4
Ooi, 2000	*	*		*		*	*	*	*	7
Shaw, 2015	*	*	*	*						4
Tinetti, 1986	*	*					*		*	4
Patients with Parkinson's disease										
François, 2017	*	*								2
Gray, 2000	*	*					*		*	4
Kerr, 2010	*						*	*		3
Koller, 1989	*	*								2
Matinolli, 2009	*	*		*			*			4
Merola, 2016	*	*		*			*			4
Rascol, 2015	*	*								2
Sithinamsuwan, 2010	*	*		*			*			4
Patients with specific other diseases										
Azidah, 2012	*	*		*						3
Galizia, 2013	*	*		*						3
Joo, 2002	*				*	*	*		*	5
Kadir, 2011	*				*	*				3
Shen, 2015	*	*		*	*	*	*			6
Van Hateren, 2012	*			*	*	*				4
Van Helden, 2007	*	*		*			*		*	5

*: Attributed point

Part II

The clinical value of parameters derived from continuous orthostatic blood pressure measurements

Chapter 4

Rapid systolic blood pressure changes after standing up associate with impaired physical performance in geriatric outpatients

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Abstract

Background: Orthostatic hypotension (OH) is a prevalent condition in older adults and is associated with impaired physical performance and falls. The ability of older adults to compensate for rapid changes in systolic blood pressure (SBP; i.e. SBP drop rate and SBP variability) may be important for physical performance. This study investigates the association of rapid SBP changes after standing up with physical performance.

Methods: Consecutive patients who visited the Center Of Geriatric Amsterdam (COGA) in 2014 and 2015 were included. The following SBP parameters were computed in two intervals (0-15 seconds and 15-180 seconds) after standing up: steepness of steepest SBP decline ($SBP_{max\ drop\ rate}$); ratio of standing and supine SBP variability ($SBP_{variability\ ratio}$); magnitude of largest SBP drop ($SBP_{drop\ magnitude}$). Physical performance was assessed using the following measures: chair stand time (CST), timed up and go time (TUG), walking speed, handgrip strength and tandem stance performance.

Results: 109 patients (45% male; age: mean 81.7 years (SD 7.0)) were included. $SBP_{max\ drop\ rate}$ (0-15 seconds) was associated with slower CST ($p < 0.001$), TUG ($p = 0.022$) and walking speed ($p = 0.024$). $SBP_{variability\ ratio}$ (0-15 seconds) was associated with slower CST ($p = 0.005$). $SBP_{drop\ magnitude}$ was not associated with physical performance.

Conclusions: SBP parameters reflecting rapid systolic blood pressure changes were more strongly associated with physical performance compared to SBP drop magnitude in geriatric outpatients. These results support the hypothesis of an inadequate cerebral autoregulation during rapid SBP changes and advocate the use of continuous BP measurements.

Introduction

Orthostatic hypotension (OH) is defined as a systolic blood pressure (SBP) drop of at least 20 mmHg systolic and/or a diastolic blood pressure (DBP) drop of at least 10 mmHg within 3 minutes after standing up[1] and is associated with detrimental outcome, such as increased risk of falls,[2] cardiovascular disease[3,4] and mortality.[3–7] OH affects 5-59% of adults aged 65 years and older.[8–10] OH is also associated with functional impairment and symptoms of light-headedness, dizziness and the feeling of fainting,[11,12] which may be caused by cerebral hypoperfusion and decreased brain oxygenation due to a blood pressure (BP) drop after postural change.[12–17] Posture related BP drops are counteracted by cerebral autoregulation in physiological conditions. However, cerebral autoregulation is often impaired in older adults,[18,19] potentially leading to aforementioned OH symptoms, but also impaired physical and cognitive performance.[20–23]

Cerebral autoregulation acts as a high pass filter, implying that cerebral blood flow (CBF) can be poorly regulated during rapid changes (> 0.05 Hz) in SBP.[24] CBF oscillations as a response to SBP drops induced by rapid repetitive postural changes were reported to have an higher amplitude in older adults compared to young or middle aged adults.[25] This suggests that the brain at older age is less able to compensate for rapid BP changes, as can be measured using continuous BP (cBP) measurement. This is supported by the finding that initial OH (iOH), which is a rapid BP drop (SBP drop > 40 mmHg or DBP drop > 20 mmHg) within 15 seconds after standing up, is associated with worse physical performance in geriatric outpatients.[26] iOH can only be assessed using continuous, beat-to-beat SBP measurements. The ratio of standing SBP variability and supine SBP variability ($SBP_{variability\ ratio}$) is another measure of beat-to-beat SBP changes, and was reported to be associated with falls in geriatric outpatients.[27] As measures expressing the magnitude of the SBP drop after standing weakly associate with physical performance,[12,28–31] SBP parameters expressing rapid blood pressure changes after standing up and therewith potentially reflecting cerebral hypoperfusion may be associated with worse physical performance and predict its decline. However, these associations have not yet been investigated.

The aim of this study was to compare the associations of SBP drop rate after standing up, SBP variability in supine relative to standing position and SBP drop magnitude after standing up with different physical performance measures in geriatric outpatients. It is hypothesized that the rate of SBP drop after standing up and SBP variability in supine relative to standing position rather than the magnitude of the SBP drop after standing up associate with impaired physical performance in geriatric outpatients.

Methods

The data and methods supporting the findings in the article are available from the corresponding author on reasonable request.

Setting and study population

The data of the Center of Geriatrics Amsterdam (COGA) cohort were used for this study. The COGA cohort included all patients referred to the geriatric outpatient clinic of the VU Medical Center, Amsterdam, The Netherlands, from January 2014 until December 2015, for cognitive, mobility or combined problems and underwent a comprehensive geriatric assessment (CGA). For the present analysis, patients were selected for whom physical performance was assessed and continuous BP measurements during standing up were available. This study was performed in accordance with the declaration of Helsinki (1964) and approved by the local medical ethical committee of the VU Medical Center, Amsterdam, The Netherlands. All subjects gave informed consent.

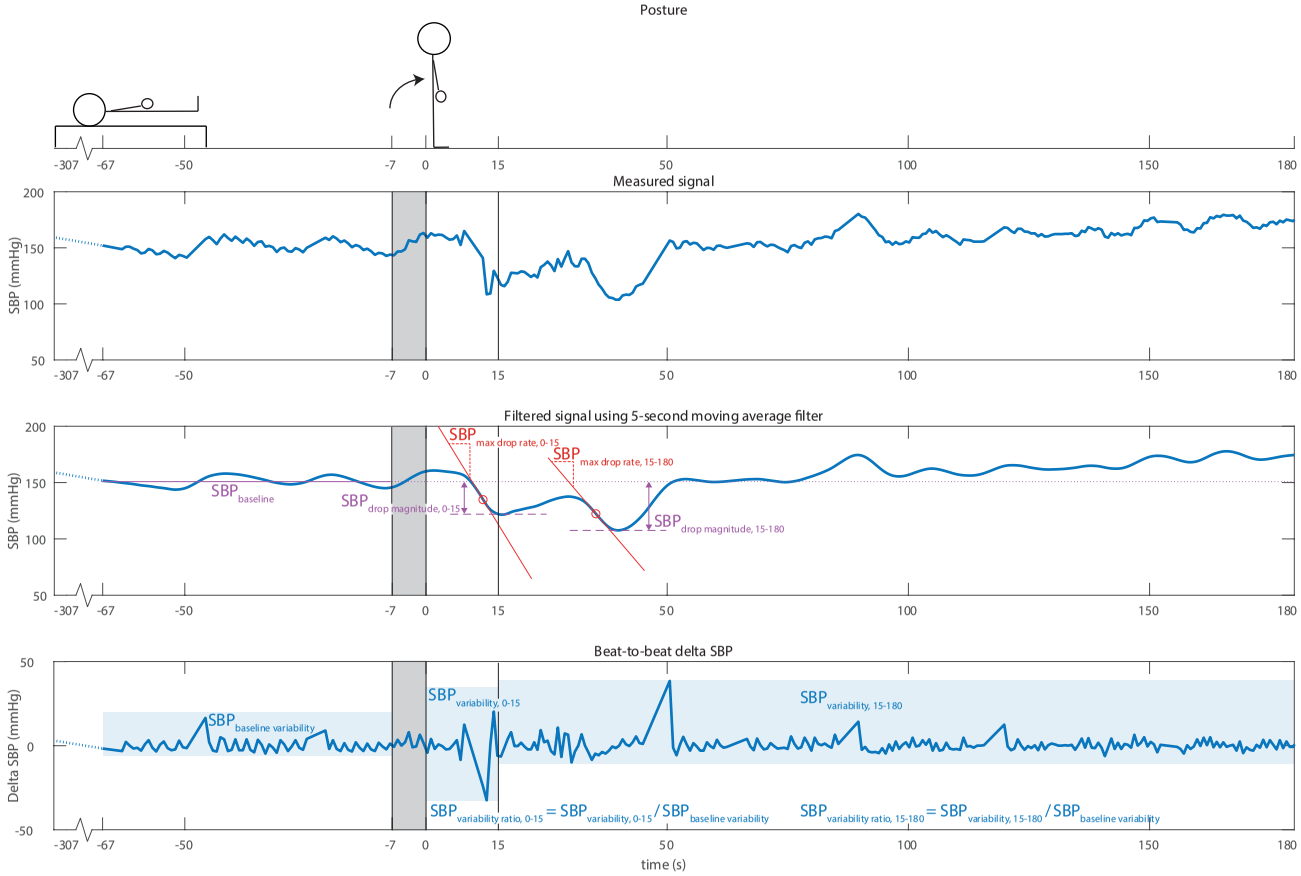

Figure 4.1. Example of continuous systolic blood pressure (SBP) before, during and after standing up in one patient. The interval from -67 – -7 seconds represents baseline (supine position), -7 – 0 seconds (gray shaded) represents the transition from supine to standing position and 0 – 180s represents the standing position period. SBPmax drop rate is defined as the steepness of the steepest negative tangent line (red lines) in the standing intervals (0-15 and 15-180 seconds). SBPdrop magnitude is defined as the difference between baseline SBP (purple dotted line) and the lowest measured SBP value in the standing intervals (purple dashed lines). SBPvariability is defined as the standard deviation of the indicated intervals. SBPvariability ratio is defined as the variability in the standing intervals divided by baseline variability.

Patient characteristics

Information on patient characteristics, such as living situation, education level, smoking habits and alcohol consumption was obtained using questionnaires. Information on age, medical history and medication use was extracted from the medical records. Body mass index and cognitive assessment using the Mini Mental State Examination (MMSE) were performed as part of the comprehensive geriatric assessment (CGA).

Blood pressure measurements

Continuous BP measurements were performed non-invasively using a digital photoplethysmograph on the right middle finger (Nexfin®, BMEYE, Amsterdam, The Netherlands), resulting in beat-to-beat BP data. Patients were instructed not to talk during the measurement. They were asked to lie supine for five minutes and subsequently to stand up without further assistance. The time instance when a patient stood independently was marked in the data. Patients were asked to keep standing for three minutes. BP was also assessed intermittently before and 1 and 3 minutes after standing up using a sphygmomanometer.

Blood pressure data analysis

BP data were analyzed using MATLAB R2017b (The Mathworks Inc., Natick, Massachusetts, USA). BP data were excluded if they were incomplete (baseline < 30 seconds or standing time < 150 seconds) or very noisy on inspection. The records were divided into three epochs: (1) resting, (2) transition, (3) standing, as shown in figure 4.1. The resting epoch was defined as the 60 seconds before the start of the transition epoch, which was assumed to have a length of 7 seconds [32], ending at the instance of the standing marker. The standing epoch was defined as the time from the standing marker to 180 seconds later.

Baseline SBP was computed as the mean of the 60-second resting epoch. A 5-second window moving average filter was applied to the SBP signal to attenuate artifacts.[33] The filtered SBP signal was used to compute the rate of SBP drop ($SBP_{max\ drop\ rate}$), which was defined as the largest amplitude of the negative peak in the first derivative of SBP. SBP variability ratio ($SBP_{variability\ ratio}$) was computed as the ratio of standing variability to supine variability. Variability was defined as the standard deviation of the difference between adjacent SBP values (delta SBP).[27] The size of the SBP drop ($SBP_{drop\ magnitude}$) was defined as the magnitude of the largest drop in SBP compared to baseline in the filtered SBP signal. The derivation of the SBP parameters from the SBP data is illustrated in figure 4.1. All SBP parameters were computed for two intervals: 0-15 seconds and 15-80 seconds after standing, resulting in six SBP parameters: $SBP_{max\ drop\ rate,\ 0\text{-}15}$, $SBP_{max\ drop\ rate,\ 15\text{-}180}$, $SBP_{variability\ ratio,\ 0\text{-}15}$, $SBP_{variability\ ratio,\ 15\text{-}180}$, $SBP_{drop\ magnitude,\ 0\text{-}15}$ and $SBP_{drop\ magnitude,\ 15\text{-}180}$.

Physical performance

Physical performance was assessed using the following measures dynamic measures (i.e. involving postural changes): chair stand time (CST), timed up and go time (TUG); and static measures: walking speed, handgrip strength (HGS) and performance on the tandem stance test. CST was available for 79 patients, TUG for 68 patients, walking speed for 99 patients, HGS for 96 patients and tandem stance performance for 100 patients. CST is the time in seconds needed to stand up from sitting position (knees in 90 degrees flexion) five times as rapid as possible without the use of hands, as defined in the Short Physical Performance Battery (SPPB).[34] TUG is the time in seconds needed to stand up from sitting position without the use of hands, walk around a cone and sit down in starting position.[35] The 4-meter walk test was used to assess normal pace walking speed (m/s) on a standardized 4-meter distance walking path. It was performed twice according to the SPPB,[34] of which the fastest speed was used for the analysis. HGS (kg) was assessed three times for both hands, in the standing position with the arm parallel to the body, using a handheld hydraulic dynamometer.[36] The maximal HGS was used for the analysis. Performance on the tandem test with eyes open was used to represent balance performance, and defined as the ability or disability to maintain tandem position for 10 seconds.

Statistical analysis

Continuous variables were presented as means and standard deviations (SD) if the data was normally distributed and as medians and interquartile ranges in other cases. SBP parameters were normalized to enable comparing regression betas or ORs. The log transformation was applied to CST and TUG (logCST and logTUG, respectively) to obtain normal distributions. The association between normalized SBP parameters and physical performance was analyzed using linear regression analysis (CST, TUG, walking speed, HGS) and logistic regression analysis (tandem stance tests). All regression analyses were adjusted for age, sex, height and weight. To account for large differences in HGS between sexes, we normalized HGS within each sex. Additional adjustment for maximum increase in heart rate, as an indicator for baroreflex function, was performed in separate regression models.

Statistical analyses were performed in Statistical Package for the Social Sciences (SPSS version 22), using a significance level of 0.05. As the association of six SBP parameters with five physical performance outcomes was tested, correction for 30 comparisons was performed according to the Bonferroni method.

Results

Continuous BP and physical performance data were available for 109 geriatric outpatients, of whom the characteristics are presented in table 4.1. The participants included in the presents study did not differ significantly with respect to demographics and health characteristics from other patients in the COGA database for whom no physical performance or continuous BP data were available. Mean resting supine SBP and DBP in these patients were 132.7 (SD 27.0) and 68.6 (SD 11.2) mmHg, respectively. When BP was measured intermittently, OH was present in 41.1% of the patients. OH was present in 76.1% and iOH in 29.4% of the patients when BP was measured continuously.

Table 4.2 presents the association between continuously measured BP and

Table 4.1. Patient characteristics

Characteristic	N	All (n = 109)
Age, years, mean (SD)	109	81.7 (7.0)
Male, n (%)	109	49 (45.0)
Living at home, n (%)	105	90 (85.7)
Current smoking, n (%)	103	13 (12.6)
Highly educated*, n (%)	105	18 (17.1)
Excessive alcohol use†, n (%)	95	8 (8.4)
Multimorbidity‡, n (%)	109	51 (46.8)
BMI, kg/m^2, mean (SD)	105	26.2 (7.5)
MMSE, median, [IQR]	100	27.0 [24.0 – 29.0]
Number of medications, median, [IQR]	104	7.0 [4.0 – 9.0]
Systolic in mmHg, mean (SD)	109	132.7 (27.0)
Diastolic in mmHg, mean (SD)	109	68.6 (11.2)
Orthostatic BP and HR responses		
$OH_{intermittently}$, n (%)	73	30 (41.1)
$OH_{continuously}$, n (%)	109	83 (76.1)
iOH, n (%)	109	32 (29.4)
$SBP_{drop\ rate}$ 0-15s in mmHg/s, median [IQR]	109	-2.53 [-4.97 - -0.86]
$SBP_{drop\ rate}$ 15-180s in mmHg/s, median [IQR]	109	-2.96 [-4.48 - -2.13]
$SBP_{variability\ ratio}$ 0-15s, median [IQR]	109	1.03 [0.57 – 2.14]
$SBP_{variability\ ratio}$ 15-180s, median [IQR]	109	0.909 [0.51 – 1.35]
$SBP_{drop\ magnitude}$ 0-15s in mmHg, mean (SD)	109	27.6 (24.3)
$SBP_{drop\ magnitude}$ 15-180s in mmHg, mean (SD)	109	26.4 (31.3)
HR increase 0-180s in 1/s, median [IQR]	109	23.9 [11.28 – 29.4]
Physical performance		
CST in s, median [IQR]	79	13.7 [10.9 – 17.8]
TUG in s, median [IQR]	68	15.0 [11.1 – 18.0]
Walking speed on 4m walk test in m/s, mean (SD)	99	0.80 (0.32)
HGS males in kg, mean (SD)	44	26.0 (8.7)
HGS females in kg, mean (SD)	52	13.3 (7.1)
Side-by-side stance, able to maintain, n (%)	101	90 (89.1)
Semi-tandem stance, able to maintain, n (%)	101	77 (76.2)
Tandem stance, able to maintain, n (%)	100	37 (37.0)

SD: standard deviation; BMI: body mass index; MMSE: mini mental state examination; IQR: interquartile range; $OH_{intermittently}$ / $OH_{continuously}$: prevalence of OH assessed using intermittent / continuous BP measurements; iOH: initial orthostatic hypotension; SBP: systolic blood pressure; HR: heart rate; CST: chair stand time; TUG: timed up and go time; HGS: handgrip strength; *Highly educated is defined as having a university degree. †Excessive alcohol use is defined as >14 units per week for females and > 21 units per week for males. ‡Multimorbidity is defined as two or more diseases of the following: chronic obstructive pulmonary disease, diabetes mellitus, hypertension, malignancy, myocardial infarction, Parkinson's disease, rheumatoid/(osteo)arthritis. §Continuously measured

physical performance. $SBP_{max\ drop\ rate,\ 0\text{-}15}$ was associated with impaired performance on the CST ($p < 0.001$), TUG ($p = 0.022$) and walking speed ($p = 0.024$). $SBP_{variability\ ratio,\ 0\text{-}15}$ was associated with impaired performance on the CST ($p = 0.005$). $SBP_{drop\ magnitude,\ 0\text{-}15}$ was not associated with physical performance. None of the SBP parameters reflecting the 15-180 second interval after standing were associated with physical performance. None of the SBP parameters were associated with HGS, either before or after normalization within each sex, or with balance performance. After correction for multiple comparisons, all associations lost significance, except the association of $SBP_{max\ drop\ rate,\ 0\text{-}15}$ with CST.

Maximum heart rate increase after standing up was associated with $SBP_{max\ drop\ rate,\ 15\text{-}180}$, $SBP_{variability\ ratio,\ 0\text{-}15}$ and $SBP_{variability\ ratio,\ 15\text{-}180}$, but not with other SBP parameters or physical performance (Table 4.3 and 4.4). Correction of the association between SBP parameters and physical performance for maximum heart rate increase did not change the statistical significance of the found associations (Table 4.5).

Discussion

In a population of geriatric outpatients, the rate of systolic blood pressure (SBP) drop within 15 seconds after standing was significantly associated with impaired dynamic physical performance (chair stand test, timed up and go test) and a lower walking speed. Furthermore, the variability of SBP in standing relative to supine position within 15 seconds after standing was associated with impaired performance on the chair stand test. In contrast, the magnitude of SBP drop was not associated with physical performance. None of the SBP parameters reflecting the 15-180 second interval after standing up were associated with physical performance and no SBP parameters were associated with handgrip strength and balance performance. After correction for multiple comparisons, only the association of SBP drop rate with chair stand time remained significant.

The results support the hypothesis that the rate of SBP drop rather than the magnitude of the SBP drop associate with physical performance in geriatric outpatients. To the best of our knowledge, this is the first study that addresses the association of measures expressing the rate of SBP drop after standing up and the variability of SBP in the standing relative to supine position with physical performance in a clinically relevant population of geriatric outpatients. The results of the present study are in concordance with studies reporting the absence of an association between OH (which is defined in terms of the magnitude of SBP and DBP drop) and TUG.[12,29–31]

The results suggest that rapid SBP changes rather than large SBP changes may be a potential cause of physical performance impairment, as they may be a larger challenge to cerebral autoregulation.[37] The resulting drop in cerebral blood flow may cause impaired physical performance through several pathophysiological

Table 4.2. Continuously measured BP and physical performance

		Dynamic physical performance		Static physical performance		
		logCST (s; n = 79)	**logTUG (s; n = 68)**	**Walking speed (m/s; n = 99)**	**HGS (kg, n = 96)**	**Tandem stance (% able; n = 100)**
$SBP_{max\ drop\ rate,\ 0\text{-}15}$	*β / OR*	0.177 (*β*)	0.105 (*β*)	-0.066 (*β*)	0.123 (*β*)	0.603 (OR)
	95% CI	0.085 – 0.269	0.016 – 0.195	-0.123 – -0.009	-1.330 – 1.575	0.186 – 1.957
	p	<0.001	0.022*	0.024*	0.876	0.400
$SBP_{variability\ ratio,\ 0\text{-}15}$	*β / OR*	0.121 (*β*)	0.069 (*β*)	-0.010 (*β*)	-0.107 (*β*)	0.971 (OR)
	95% CI	0.038 – 0.205	-0.017 – 0.155	-0.069 – 0.048	-1.504 – 1.290	0.632 – 1.491
	p	0.005*	0.112	0.726	0.879	0.893
$SBP_{drop\ magnitude,\ 0\text{-}15}$	*β / OR*	0.032 (*β*)	-0.007 (*β*)	0.005 (*β*)	-0.109 (*β*)	0.627 (OR)
	95% CI	-0.072 – 0.136	-0.105 – 0.091	-0.054 – 0.064	-1.643 – 1.425	0.196 – 2.010
	p	0.538	0.887	0.876	0.888	0.433
$SBP_{max\ drop\ rate,\ 15\text{-}180}$	*β / OR*	-0.011 (*β*)	-0.011 (*β*)	0.002 (*β*)	0.348 (*β*)	0.634 (OR)
	95% CI	-0.106 – 0.084	-0.097 – 0.075	-0.055 – 0.060	-1.051 – 1.820	0.198 – 2.029
	p	0.818	0.797	0.935	0.596	0.443
$SBP_{variability\ ratio,\ 15\text{-}180}$	*β / OR*	0.003 (*β*)	-0.023 (*β*)	0.029 (*β*)	0.951 (*β*)	0.694 (OR)
	95% CI	-0.094 – 0.099	-0.110 – 0.064	-0.030 – 0.088	-0.524 – 2.425	0.412 – 1.169
	p	0.953	0.598	0.336	0.204	0.169
$SBP_{drop\ magnitude,\ 15\text{-}180}$	*β / OR*	0.044 (*β*)	-0.013 (*β*)	-0.029 (*β*)	-1.632 (*β*)	1.182 (OR)
	95% CI	-0.077 – 0.165	-0.129 – 0.102	-0.096 – 0.039	-3.525 – 0.106	0.730 – 1.915
	p	0.475	0.819	0.404	0.065	0.497

SBP: systolic blood pressure; logCST: logarithm of chair stand time in seconds; logTUG: logarithm of timed up and go time in seconds; HGS: handgrip strength; OR: odds ratio; CI: confidence interval. $SBP_{max\ drop\ rate}$, $SBP_{variability\ ratio}$ and $SBP_{drop\ magnitude}$ were normalized to enable comparing betas / ORs. CST, TUG, walking speed and HGS data are from linear regression analyses with adjustments for age, sex, height and weight and reported using regression betas. Balance data are from logistic regression analyses with adjustments for the same factors and reported using ORs. *This association does not remain significant after correction for multiple comparisons.

mechanisms: 1) an acute brain perfusion drop after standing,[13,14] which may manifest within minutes after postural change; 2) chronic brain pathology, such as brain atrophy, microbleeds and white matter brain lesions,[38,39,48,40–47] which may manifest over months to years. Decreased brain perfusion was found to be associated with worse lower extremity function, slower gait speed and orthostatic symptoms in previous studies, indicating the clinical importance of cerebral blood flow drops.[20,21,23] Continuous BP measurements may provide an indication of cerebral blood flow drops, as suggested by the present study.

The results may be partly explained by atherosclerosis as a common mechanism causing both baroreflex dysfunction by impaired stretch of the baroreceptors and impaired physical performance due to compromised cerebral vasculature.[49–51] In the investigated population, atherosclerosis and resulting high vessel stiffness is likely to be prevalent, as suggested by the low DBP and high difference between resting SBP and DBP (i.e. pulse pressure).[52] Baroreflex dysfunction would be reflected by a blunted heart rate increase after standing up.[53] However, heart rate increase after standing up in the investigated population was comparable to community dwelling older adults. [54] Furthermore, baroreflex dysfunction due to atherosclerosis does not

Table 4.3. Maximum heart rate increase after standing up and SBP parameters

		$logSBP_{max\ drop\ rate}$ (mmHg/s; n = 109)	**$logSBP_{variability\ ratio}$ (n = 109)**	**$SBP_{drop\ magnitude}$ (mmHg; n = 109)**
$HR_{increase,\ 0\text{-}180}$			**0-15 seconds**	
	β	0.018	0.014	0.112
	95% CI	-0.027 – 0.063	0.005 – 0.022	-0.086 – 0.310
	p	0.428	**0.003**	0.264
$HR_{increase,\ 0\text{-}180}$			**15-180 seconds**	
	β	0.008	0.010	0.135
	95% CI	0.003 – 0.012	0.004 – 0.017	-0.122 – 0.392
	p	**0.002**	**0.002**	0.301

$HR_{increase,\ 0\text{-}180}$: maximum increase of heart rate within 180 seconds after standing up compared to baseline; OR: odds ratio; CI: confidence interval. $SBP_{max\ drop\ rate}$ and $SBP_{variability\ ratio}$ were log-transformed to obtain normal distributions. All data are from linear regression analyses.

Table 4.4. Maximum heart rate increase after standing up and physical performance

	Dynamic physical performance		**Static physical performance**		
	logCST (s; n = 79)	**logTUG (s; n = 68)**	**Walking speed (m/s; n = 99)**	**HGS (kg, n = 96)**	**Tandem stance (% able; n = 100)**
$HR_{increase,\ 0\text{-}180}$					
β / OR	0.003 (β)	0.003 (β)	-0.001 (β)	-0.040 (β)	0.994 (OR)
95% CI	-0.001 – 0.006	-0.001 – 0.007	-0.003 – 0.002	-0.126 – 0.045	0.975 – 1.014
p	0.166	0.164	0.635	0.355	0.576

$HR_{increase,\ 0\text{-}180}$: maximum increase of heart rate within 180 seconds after standing up compared to baseline; logCST: logarithm of chair stand time in seconds; logTUG: logarithm of timed up and go time in seconds; HGS: handgrip strength; OR: odds ratio; CI: confidence interval. CST, TUG, walking speed and HGS data are from linear regression analyses. Tandem stance data are from logistic regression analyses.

Table 4.5. Continuously measured BP and physical performance, adjusted for baroreflex function

		Dynamic physical performance		Static physical performance		
		logCST (s; n = 79)	**logTUG (s; n = 68)**	**Walking speed (m/s; n = 99)**	**HGS (kg, n = 96)**	**Tandem stance (% able; n = 100)**
$SBP_{drop\ rate,\ 0\text{-}15}$	*β / OR*	0.168 (β)	0.099 (β)	-0.065 (β)	0.185 (β)	1.026 (OR)
	95% CI	0.075 – 0.262	0.006 – 0.191	-0.124 – -0.007	-1.294 – 1.664	0.620 – 1.697
	p	0.001	0.037*	0.029*	0.804	0.921
$SBP_{variability\ ratio,\ 0\text{-}15}$	*β / OR*	0.110 (β)	0.059 (β)	-0.007 (β)	0.016 (β)	1.026 (OR)
	95% CI	0.022 – 0.198	-0.034 – 0.152	-0.068 – 0.055	-1.448 – 1.479	0.647 – 1.626
	p	0.015*	0.208	0.834	0.983	0.914
$SBP_{drop\ magnitude,\ 0\text{-}15}$	*β / OR*	0.031 (β)	-0.013 (β)	0.006 (β)	-0.091 (β)	1.154 (OR)
	95% CI	-0.072 – 0.134	-0.112 – 0.085	-0.054 – 0.065	-1.634 – 1.452	0.704 – 1.891
	p	0.555	0.785	0.843	0.907	0.570
$SBP_{drop\ rate,\ 15\text{-}180}$	*β / OR*	0.038 (β)	-0.042 (β)	0.007 (β)	0.585 (β)	0.796 (OR)
	95% CI	-0.151 – 0.053	-0.139 – 0.054	-0.055 – 0.060	-0.960 – 2.129	0.466 – 1.360
	p	0.526	0.386	0.771	0.454	0.403
$SBP_{variability\ ratio,\ 15\text{-}180}$	*β / OR*	-0.033 (β)	-0.059 (β)	0.041 (β)	1.276 (β)	0.702 (OR)
	95% CI	-0.137 – 0.071	-0.156 – 0.039	-0.053 – 0.071	-0.321 – 2.874	0.400 – 1.234
	p	0.531	0.235	0.207	0.116	0.485
$SBP_{drop\ magnitude,\ 15\text{-}180}$	*β / OR*	0.035 (β)	-0.018 (β)	-0.027 (β)	-1.601 (β)	0.986 (OR)
	95% CI	-0.082 – 0.159	-0.133 – 0.098	-0.096 – 0.041	-3.344 – 0.141	0.562 – 1.728
	p	0.499	0.760	0.432	0.071	0.961

SBP: systolic blood pressure; logCST: logarithm of chair stand time in seconds; logTUG: logarithm of timed up and go time in seconds; HGS: handgrip strength; OR: odds ratio; CI: confidence interval. $SBP_{drop\ rate}$, $SBP_{variability\ ratio}$ and $SBP_{drop\ magnitude}$ were normalized to enable comparing betas / ORs. CST, TUG, walking speed and HGS data are from linear regression analyses with adjustments for age, sex, height, weight and maximum increase of heart rate within 180 seconds after standing up compared to baseline, and reported using regression betas. Tandem stance data are from logistic regression analyses with adjustments for the same factors and reported using ORs. *This association does not remain significant after correction for multiple comparisons.

fully explain the found association, as this remained significant after correction for maximum increase of heart rate after standing up.

Apart from baroreflex dysfunction, mechanisms leading to impaired cardiac output, such as volume depletion, congestive heart failure, and calf muscle deconditioning may increase $SBP_{max\ drop\ rate}$ and $SBP_{variability\ ratio}$.[55] Furthermore, increased vessel stiffness may prevent appropriate vasoconstriction after standing up, potentially leading to rapid SBP changes.[56]

$SBP_{max\ drop\ rate}$, reflecting the rate of SBP drop after standing, was associated with dynamic measures of physical performance (i.e. involving one or more postural changes) rather than static measures. Though it is uncertain whether rapid SBP changes occurred during the assessment of dynamic physical performance, this finding suggests an immediate negative influence of rapid SBP changes after standing up on dynamic physical performance.

Systolic BP rather than diastolic BP was analyzed in this study, as systolic BP variations were reported to be associated stronger with cerebral blood flow velocity during standing up than diastolic blood pressure.[24] Furthermore, variability in systolic BP was reported to be associated with falls rather than diastolic blood pressure.[27]

OH prevalence, as assessed using continuous BP measurements, was found to be much higher than OH prevalence assessed using intermittent BP measurements, suggesting that the OH may be underdiagnosed when using intermittent BP which substantiates previous findings.[17] As OH is associated with falls,[2] cardiovascular disease[3,4] and mortality[3–7], this might have clinical consequences due to undertreatment. However, OH treatment effectiveness has not been adequately established using continuous BP measurement.

Clinical implications

This study provides an indication that parameters expressing rapid SBP changes after standing up may reflect a failing cerebral autoregulation and potentially predict physical performance decline. The results underpin the clinical value of continuous BP measurements, which are needed to compute these parameters.

Strength and limitations

The strength of this study is that it assesses the clinical relevance of SBP parameters expressing rapid SBP changes after standing up in a clinically relevant population of geriatric outpatients using a variety of physical performance tests, ranging from dynamic to static. Though the results suggest an inadequate cerebral autoregulation being at play, further evidence is needed, e.g. by simultaneous measurements of BP, cerebral oxygenation and physical performance. This study does not provide evidence for a longitudinal association between SBP parameters and physical performance and does not provide data on cerebral blood flow during standing up to assess cerebral autoregulation function. Furthermore, due to multiple comparisons,

uncorrected p- values should be interpreted with care and may require further confirmation by future studies.

Conclusion

SBP parameters reflecting rapid systolic blood pressure changes were more strongly associated with physical performance compared to SBP drop magnitude in geriatric outpatients. The association between rapid SBP changes and dynamic physical performance suggests an inadequate cerebral autoregulation during rapid SBP changes after standing up and underpins the value of continuous BP measurements, which are needed to measure rapid SBP changes. Future research should address the value of these SBP parameters to predict physical functioning decline in longitudinal studies. Investigation of the role of cerebral autoregulation requires transcranial Doppler or near-infrared spectroscopy measurements. Multimodal, synchronous and unobtrusive measurements assessing different parts of the cardiovascular system may provide insight in the pathophysiological mechanisms and potential clinical consequences of OH.

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Chapter 5

Blood pressure drop rate after standing up is associated with frailty and number of falls in geriatric outpatients

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Abstract

Background: The relationship between orthostatic hypotension and clinical outcome in older adults is poorly understood. Blood pressure drop rate (i.e. speed of blood pressure drop) may particularly reflect the imposed challenge to the baroreflex and the associated clinical outcome (i.e. frailty and number of falls). This study aimed to compare orthostatic blood pressure drop rate and drop magnitude with regard to their association with frailty and number of falls.

Methods: Blood pressure was measured continuously during a standardized active stand task in 168 patients (mean age 81.4 ± 7.0; 55.4% female) who visited a geriatric outpatient clinic for cognitive or mobility problems. The association of orthostatic blood pressure drop rate, blood pressure drop magnitude and baroreflex sensitivity (i.e. increase in heart rate divided by SBP drop magnitude) with frailty (Fried criteria and four frailty markers) and self-reported number of falls was assessed using linear regression models, adjusting for age and sex.

Results: Systolic blood pressure drop rate had the strongest association with frailty according to the four frailty markers (β 0.30, 95% confidence interval (CI) 0.11-0.49, p 0.003) and number of falls (β 1.09, 95% CI 0.19 – 1.20, p 0.018); diastolic blood pressure drop magnitude was strongest associated with frailty according to the Fried criteria (β 0.37, 95% CI 0.15 – 0.60, p 0.001). Baroreflex sensitivity was associated with neither frailty nor number of falls.

Conclusions: Orthostatic blood pressure drop rate was associated with frailty and falls, and may reflect the challenge to the baroreflex rather than drop magnitude.

Introduction

Orthostatic hypotension (OH), defined as a systolic blood pressure (SBP) drop of 20 mmHg or a diastolic blood pressure (DBP) drop of 10 mmHg within three minutes after standing up, occurs in 5% to 30% of adults above 65 years of age and is associated with impaired physical and cognitive functioning, cardiovascular disease and mortality.[1–4] However, these associations are poorly understood and may be determined by the blood pressure (BP) challenge imposed to the baroreflex as well as baroreflex sensitivity (BRS, i.e. heart rate increase relative to BP drop).[5,6]

Continuous beat-to-beat BP were shown to be of additional clinical value compared to intermittent BP measurements.[5,7] The imposed challenge to the baroreflex may be particularly reflected by BP drop rate (i.e. the speed of BP drop after standing up), as the baroreflex has a latency to reach its peak potential.[8,9] A large imposed challenge to the baroreflex might due to baroreflex latency cause a temporary decrease of cardiac output[10], hypoperfusion of the brain, retina and muscles[11] and acute symptoms of dizziness, fainting, blurry vision and falls.[4] Recurrent brain hypoperfusion may lead to cognitive impairment[2], mobility limitations,

impaired activities of daily living[1], loss of muscle mass, lower physical activity and exhaustion, which are reflected by the Fried and the four frailty markers.[12] Previous studies reported an association of OH with frailty or falls,[7,13–23] but did not assess the association of BP drop rate with frailty or falls.

The objective of this study was to compare BP drop rate after standing up with BP drop magnitude and BRS with regard to their association with frailty and number of falls in group of geriatric outpatients with a high prevalence of OH. It was hypothesized that BP drop rate is associated with frailty and number of falls.

Methods

Study design and setting

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data from two patient groups (Bronovo and COGA) were used. The Bronovo patient group included patients referred to the geriatric outpatient clinic of the Bronovo hospital (The Hague, the Netherlands) between March 2011 and January 2012. The COGA patient group included patients referred to the Center of Geriatrics in Amsterdam (COGA) of the VU University Medical Center Amsterdam (Amsterdam, the Netherlands) between January 2014 and December 2015. Patients visiting the outpatient clinic for cognitive or mobility problems after referral by a general practitioner underwent a comprehensive geriatric assessment (CGA).

Ethical approval and informed consent

This study was performed in accordance with the Declaration of Helsinki and approved by the local medical ethical committee of the VU University Medical Center Amsterdam (COGA patient group) and the institutional review board of the Leiden University Medical Centre (Bronovo patient group). For both patient groups, informed consent was waived, as the data was collected as part of usual clinical care.

Patient characteristics

Information about age, sex, height, weight, medical history, medication, living situation, smoking habits and alcohol consumption were extracted from the medical records. The Mini Mental State Examination (MMSE©, Par Inc, USA) was used to assess cognitive performance.[24] Subdomains assessed by the MMSE include orientation to time and place, attention, calculation, recall, language, repetition and complex commands. Multi-morbidity was defined as two or more of the following diseases diagnosed and described in the patients' medical record by the geriatrician: chronic obstructive pulmonary disease, diabetes mellitus, hypertension, malignancy, myocardial infarction, Parkinson's disease, (osteo)arthritis.

Blood pressure measurement

A subpopulation of patients underwent continuous blood pressure measurements during standing up from supine to standing position, depending on the availability of the equipment. Beat-to-beat blood pressure was measured using a finger photoplethysmograph (Nexfin; BMEYE, Amsterdam, the Netherlands). Patients were asked to lie down in a supine position for 5 minutes after which they were asked to stand up and continue standing for 3 minutes. Standing up was supported by an automatic lift chair (Vario 570, Fitform B.V. Best, The Netherlands) in the Bronovo patient group, and performed unsupported in the COGA patient group. The moment of standing was marked in the data. Blood pressure was also measured intermittently in a supine position and at 1 and 3 minutes after standing up using a sphygmomanometer.

Frailty and number of falls

The Fried criteria and the four frailty markers were used to assess frailty. The Fried criteria assess unintentional weight loss, exhaustion, physical inactivity, gait speed, and handgrip strength and attribute one point for each frailty item (1 point per item, max. 5 points), more points indicating higher frailty.[12] Patients were considered non-frail, pre-frail or frail according to the Fried frailty criteria if they scored 0, 1-2 or 3-5 points, respectively.[12]

The four frailty markers assess mobility, incontinence, cognitive function and activities of daily living (ADL; 1 point per item, max 4 points).[25] Patients were considered non-frail, pre-frail or frail according to the four frailty markers if they scored 0-1, 2 or 3-4 points, respectively.[25]

Weight loss was defined as a patient-reported loss of more than 3 kg in the previous month or more than 6 kg in the previous 6 months.[26] Exhaustion was assessed by the individual question ‘I feel as if I am slowed down’ answered with ‘very often’ or ‘nearly all the time’ on the Hospital Anxiety and Depression Scale.[26,27] Physically inactive was defined as a patient-reported maximum distance of outdoor walking less than 20 minutes, only walking indoors, or not walking at all.[26] Gait speed was assessed using the 4-meter walk test.[26] Handgrip strength was defined as maximal force in kilograms of 3 performances on each hand, by using hand-held dynamometry (JAMAR hand dynamometer; Sammons Preston, Inc., Bolingbrook, IL).[26] Mobility impairment was defined as the patient-reported use of a walking aid or need for assistance with walking.[26] ADL was assessed using the Katz index, excluding the incontinence item as incontinence is a separate item in the four frailty markers.[26,28] Incontinence was defined as the patient-reported incontinence of either bladder or bowel.[26] Cognitive impairment was defined as a score below 24 points on the MMSE.[26]

Number of falls was assessed by asking patients how many times they fell in the past year.

Blood pressure and heart rate signal analysis

All BP and HR signal analyses were performed using MATLAB R2017b (the Mathworks Inc., Natrick, MA). Signals were excluded if they were incomplete (baseline < 30 seconds or standing time < 150 seconds) or very noisy on inspection. Signals were filtered using a 5-second window moving average filter and split into three epochs; resting (60 seconds), transition (7 seconds) and standing (180 seconds). The separation between the transition and standing epochs was manually marked during the test. Baseline was defined as the mean of the 60-second resting epoch. BP drop rate was defined as the largest amplitude of the negative peak in the first derivative of BP and BP drop magnitude as the magnitude of the largest decline in BP compared to the baseline, as demonstrated in a previous study.[5] All BP parameters were assessed both in the 0-15 and 15-180 second interval after standing up, resulting in eight BP parameters: $SBP_{drop\_rate\_0\text{-}15}$, $SBP_{drop\_magnitude\_0\text{-}15}$, $DBP_{drop\_rate\_0\text{-}15}$, $DBP_{drop\_magnitude\_0\text{-}15}$, $SBP_{drop\_rate\_15\text{-}180}$, $SBP_{drop\_magnitude\_15\text{-}180}$, $DBP_{drop\_rate\_15\text{-}180}$, $DBP_{drop\_magnitude\_15\text{-}180}$. Positive BP parameters indicate a blood pressure drop and negative BP parameters indicate a BP increase. Figure 4.1 demonstrates the computations for the SBP parameters.

Orthostatic heart rate increase ($HR_{max\ increase}$) was defined as the maximum HR within 15 seconds after baseline. Baroreflex sensitivity was defined as $HR_{max\ increase}$ divided by $SBP_{drop\_magnitude\_0\text{-}15}$.

Statistical analysis

All statistical analyses were conducted with the Statistical Package for the Social Science (IBM SPSS Statistics version 22, IBM Corporation, Chicago, IL). Normally distributed variables were reported using mean and standard deviation (SD), otherwise using median and interquartile range (IQR). BP and HR parameters were normalized by subtracting the mean and dividing by the standard deviation to enable comparing the effect sizes.

Linear trends in patient characteristics across quartiles of BP parameters were tested using linear regression analysis.

The associations between BP and HR parameters and frailty and number of falls were tested using multiple linear regression models with the BP/HR parameters as independent variables, frailty score and number of falls as dependent variables. For each outcome and BP parameter, three models were created. Model 1 adjusts for sex and age. Model 2 additionally adjusts for the complementary BP parameter (e.g. $SBP_{drop\_magnitude\_0\text{-}15}$ in the analysis for $SBP_{drop\_rate\_0\text{-}15}$). Model 3 adjusts for age, sex and baroreflex sensitivity. Model 4 adjusts for age, sex and baseline blood pressure. P-values below 0.05 were considered statistically significant. Differences between frailty categories (non-frail, pre-frail and frail) were assessed using logistic regression analysis, adjusting for age and sex.

Table 5.1. Patient characteristics

	N	Bronovo (N = 59)	N	COGA (N = 109)	N	All (N = 168)
Sociodemographics						
Age, mean (SD)	59	80.8 (7.1)	109	81.7 (7.0)	168	81.4 (7.0)
Female, n (%)	59	33 (55.9)	109	60 (55.0)	168	93 (55.4)
Living at home, n (%)	59	47 (79.7)	105	90 (85.7)	164	137 (83.5)
Health characteristics						
Currently smoking, n (%)	59	9 (15.3)	103	13 (12.6)	162	22 (13.6)
Excessive alcohol use, n (%)*	59	6 (10.2)	72	6 (8.3)	131	12 (9.2)
Multi-morbidity, n (%)†	57	20 (35.1)	104	50 (48.1)	161	70 (43.5)
BMI, mean (SD)	58	26.3 (4.9)	105	25.7 (4.5)	163	25.9 (4.6)
MMSE, median (IQR)	59	26.5 (25.0 - 29.0)	100	26.0 (23.0 - 28.0)	159	27.0 (24.0 - 29.0)
No. of medication, median (IQR)	58	5.4 (4.8 - 7.3)	104	7.0 (4.0 - 9.0)	162	6.0 (4.0 - 6.0)
Blood pressure and heart rate						
SBP, mean (SD), mmHg	59	148.2 (25.8)	109	132.7 (27.0)	168	138.1 (27.6)
DBP, mean (SD), mmHg	59	74.3 (15.7)	109	68.6 (11.2)	168	70.6 (13.2)
Pulse pressure, mean (SD), mmHg	59	73.9 (20.5)	109	64.1 (19.5)	168	67.6 (20.4)
HR, mean (SD), beats/min	59	72.1 (12.5)	109	70.3 (12.0)	168	70.9 (12.2)
OH, n (%)	55	37 (67.3)	109	73 (67.0)	164	110 (67.1)
$SBP_{drop\_rate\_0\text{-}15}$, median (IQR) mmHg/s	59	4.80 (2.54 – 7.55)	109	2.53 (0.86 - 4.97)	168	3.08 (1.39 – 5.79)
$SBP_{drop\_rate\_15\text{-}180}$, median (IQR) mmHg/s	59	3.15 (2.06 – 5.72)	109	2.96 (2.13 - 4.48)	168	2.98 (2.08-4.81)
$SBP_{drop\_magnitude\_0\text{-}15}$, mean (SD) mmHg	59	27.8 (23.3)	109	27.6 (24.3)	168	27.6 (23.9)
$SBP_{drop\_magnitude\_15\text{-}180}$, mean (SD) mmHg	59	24.1 (24.7)	109	26.4 (31.3)	168	25.6 (29.1)
HR increase, mean (SD) beats/min/sec	59	12.5 (7.7)	109	14.8 (15.6)	168	12.9 (12.8)
Frailty						
Fried frailty score, mean (SD)	45	1.53 (1.30)	85	2.13 (1.20)	130	1.92 (1.30)
Non-frail, n (%)	45	13 (28.9)	85	6 (7.1)	130	19 (15.6)
Pre-frail, n (%)	45	22 (48.9)	85	46 (54.1)	130	68 (52.3)
Frail, n (%)	45	10 (22.2)	85	33 (38.8)	130	43 (33.1)
Four frailty markers[1], median (IQR)	57	2.0 (0.0 – 2.0)	91	2.0 (0.0 – 2.0)	148	2.0 (0.0 – 2.0)
Non-frail, n (%)	57	25 (43.9)	91	32 (35.2)	148	57 (38.5)
Pre-frail, n (%)	57	23 (40.4)	91	39 (42.9)	148	62 (41.9)
Frail, n (%)	57	9 (15.8)	91	20 (22.0)	148	29 (19.6)
Falls in past year, n (%)	59	24 (40.7)	100	32 (32.0)	159	56 (35.2)
Number of falls, median (IQR)	53	1.0 (0.0 – 2.0)	92	2.0 (0.0 – 3.0)	145	1.0 (0.0 – 3.0)

BMI, body mass index; BP, blood pressure; IQR, interquartile range; MMSE, Mini-Mental State Examination; OH, orthostatic hypotension; SBP, systolic blood pressure; DBP, diastolic blood pressure, $SBP_{drop\_magnitude}$, the difference between baseline SBP and the lowest measured SBP value in the standing intervals at 0–15 and 15–180 seconds; SBP_{drop_rate}, the steepness of the steepest negative tangent line in the standing intervals (0–15 and 15–180 seconds); ADL, Activities of daily living. *Excessive alcohol use was defined as >14 units per week for females and >21 units per week for males. †Multimorbidity was defined as ≥ 2 diseases of the following: chronic obstructive pulmonary disease, diabetes mellitus, hypertension, malignancy, myocardial infarction, Parkinson disease, or rheumatoid/(osteo)arthritis. [1]Number of items from the four frailty markers present.

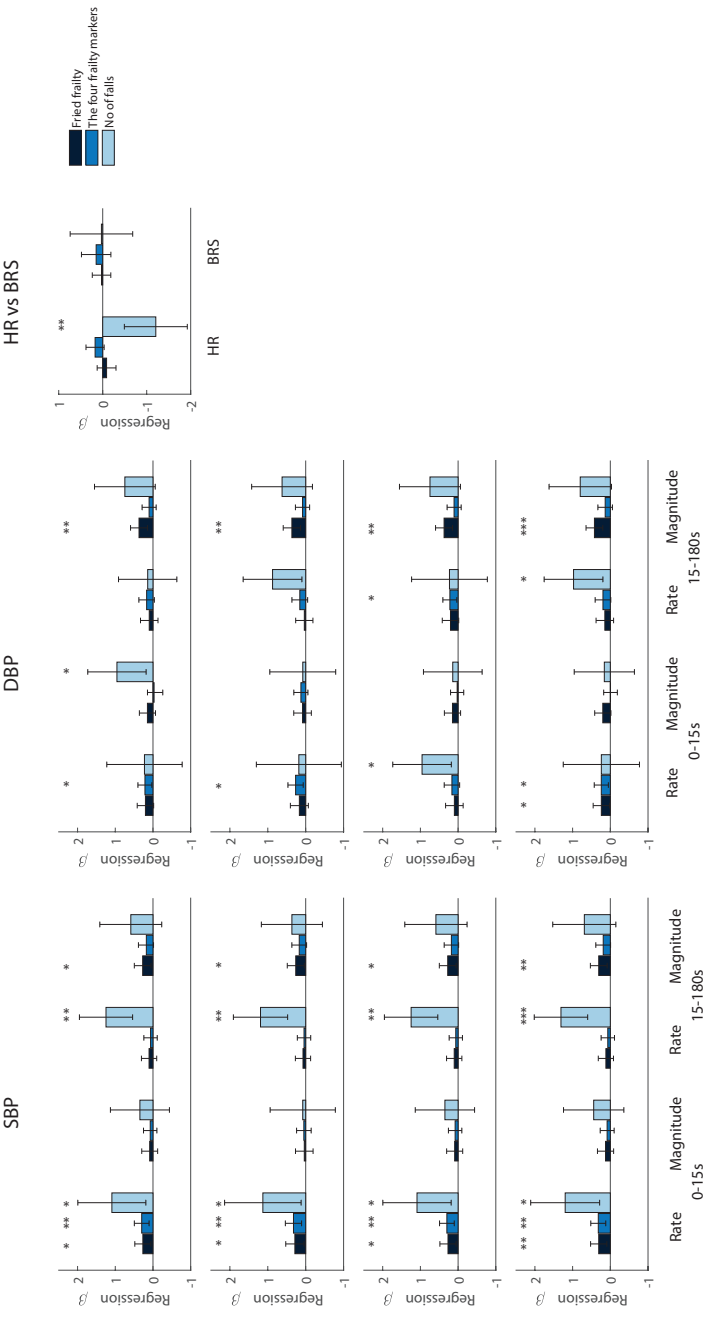

Figure 5.1. Association between BP, HR and BRS parameters and frailty and number of falls. The regression betas of the multiple linear regression analyses are shown with normalized SBP, DBP, HR and BRS parameters. Model 1 adjusts for age and sex. Model 2 additionally adjusts for the complementary BP parameter (e.g. SBPdrop_magnitude_0-15 in the analysis for SBPdrop_rate_0-15). Model 3 adjusts for age, sex and baroreflex sensitivity. Model 4 adjusts for age, sex and baseline blood pressure. The error bars indicate the 95% confidence interval. One and two stars indicate statistical significance with $p < 0.05$ and $p < 0.01$, respectively. SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; BRS: baroreflex sensitivity

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Results

Table 5.1 presents the characteristics of the 168 geriatric outpatients (59 and 109 from respectively the Bronovo and COGA cohorts) included in the analyses. The mean age of patients was 81.4 years (SD 7.0), 55.4% of the patients were female and 83.5% of the patients were living at home. Mean supine resting SBP and DBP were 139 mmHg (SD 28.8) and 70.8 mmHg (SD 13.3), respectively, and 67.1% of the patients had OH as assessed using continuous BP measurement. Mean and median frailty score according to the Fried criteria and the four frailty markers was 1.92 (SD 1.30) and 2.0 (IQR 0.0 – 2.0), respectively, and 35.2% of the population reported at least one fall in the past year with a median number of falls of 1 (IQR 0-3). Patient characteristics stratified for the different quartiles of all BP parameters are listed in supplementary tables S1 – S8 (https://rb.gy/bsfj0q).

Figure 5.1 shows the association of the BP parameters with frailty and number of falls for models 1-4, supplementary tables S9 – S12 (https://rb.gy/bsfj0q) list the strengths and confidence intervals of these associations and supplementary tables S13 and S14 (https://rb.gy/bsfj0q) show the association between BP parameters and frailty categories (non-frail, pre-frail or frail).

The following BP parameters were associated with frailty score according to the Fried criteria: $SBP_{drop\_rate\_0\text{-}15}$ (β 0.27, 95% confidence interval (CI) 0.05-0.48, p 0.015), $SBP_{drop\_magnitude\_15\text{-}180}$ (β 0.27, 95% CI 0.05 – 0.495, p 0.016) and $DBP_{drop\_magnitude\_15\text{-}180}$ (β 0.37, 95% CI 0.15 – 0.60, p 0.001). All other BP parameters showed no association with frailty score according to the Fried criteria.

The following BP parameters were associated with frailty score according to the four frailty markers: $SBP_{drop\_rate\_0\text{-}15}$ (β 0.30, 95% CI 0.11-0.49, p 0.003) and $DBP_{drop\_rate\_0\text{-}15}$ (β 0.21, 95% CI 0.03 – 0.40, p 0.024). All other BP parameters showed no association with frailty score according to the four frailty markers.

The following BP parameters were associated with number of falls: $SBP_{drop\_rate\_0\text{-}15}$ (β 1.09, 95% CI 0.19 – 1.20, p 0.018), $SBP_{drop\_rate\_15\text{-}180}$ (β 1.25, 95% CI 0.54 – 1.95, p 0.001) and $DBP_{drop\_magnitude\_0\text{-}15}$ (β 0.956, 95% CI 0.18 - 1.95, p 0.016), All other BP parameters showed no association with number of falls.

Adjusting the results for the complementary BP parameter (e.g. adjusting for $SBP_{drop\_magnitude\_0\text{-}15}$ in the analysis for $SBP_{drop\_rate\_0\text{-}15}$) in model 2 did not change the significance of the associations, except for the association between $DBP_{drop\_magnitude\_0\text{-}15}$ and number of falls, which did not remain significant. After adjusting for baroreflex sensitivity in model 3, the association between $DBP_{drop\_rate\_0\text{-}15}$ and number of falls became significant, while the association between $DBP_{drop\_magnitude\_0\text{-}15}$ and number of falls lost significance. Furthermore, the association between $DBP_{drop\_rate\_0\text{-}15}$ and the four frailty markers lost significance, while the association between $DBP_{drop\_rate\_15\text{-}180}$ and the four frailty markers became significant. Adjusting for baseline BP did not change the associations, except for the association between $DBP_{drop\_rate\_0\text{-}15}$

and frailty according to the Fried criteria, which became significant. The association between $DBP_{drop\_magnitude\_0\text{-}15}$ and number of falls lost statistical significance, while the association between $DBP_{drop\_rate\_15\text{-}180}$ and number of falls became statistically significant.

$HR_{max\ increase}$ was negatively associated with the number of falls, but not with frailty (β -1.21, 95% CI -1.92 – -0.49, p 0.001). Baroreflex sensitivity was not significantly associated with either frailty or number of falls.

Discussion

In a group of geriatric outpatients who underwent continuous BP measurements, orthostatic SBP drop rate was associated with frailty according to the four frailty markers and number of falls rather than SBP drop magnitude or DBP drop rate or magnitude, while DBP drop magnitude was strongest associated with frailty according to the Fried criteria. Baroreflex sensitivity was not associated with frailty or number of falls.

BP drop rate versus magnitude

The results partly support the hypothesis that BP drop rate rather than BP drop magnitude is associated with frailty and number of falls. No causality can be inferred from these results. A potential explanation for the results is that a rapid BP drop (i.e. high BP drop rate) may particularly reflect a challenge to the baroreflex due to an intrinsic baroreflex time delay[8,9], which might cause a temporary decrease of cardiac output[10] and brain hypoperfusion[11], which might lead to poor clinical outcome.[29] Support for causality of this relationship should be sought in further prospective intervention studies investigating the predictive value of SBP drop rate for future frailty and falls. The potential attenuating role of cerebral autoregulation in this relationship should be investigated in further studies using simultaneous measurements of continuous blood pressure and cerebral blood flow using transcranial Doppler measurements during orthostatic challenges. Alternatively, a causative relationship in the opposite direction might play a role as frailty and previous falls may lead to fear of falls and lower physical activity, resulting in rapid BP drops by general deconditioning and loss of muscle mass.

Mutual adjustment for BP drop rate and magnitude did not change the overall results, indicating the robustness of the found associations. Adjustment for baroreflex sensitivity mainly changed the association of $DBP_{drop\_rate\_0\text{-}15}$ and $DBP_{drop\_magnitude\_0\text{-}15}$ with number of falls to significant and non-significant, respectively, suggesting that BP drop rate particularly represents a challenge to the baroreflex irrespective of baroreflex sensitivity.

Baroreflex sensitivity

No association was found between baroreflex sensitivity and frailty or number of falls. This may indicate that baroreflex sensitivity has no major role in the prevention of frailty and falls, or that there was ceiling effect due to a relatively high baroreflex sensitivity in most patients. Alternatively, a more robust measure could be used for baroreflex sensitivity. In the present study, data from a single postural change was available, but baroreflex sensitivity may be measured more robustly using transfer function analysis or the sequence method analysis on blood pressure and heart rate data acquired during rhythmically repeated postural changes.[30,31] The absence of an association of baroreflex sensitivity with frailty and number of falls therefore need to be further established.

Systolic blood pressure versus diastolic blood pressure

SBP drop rate was stronger associated with number of falls and frailty than DBP drop rate, and DBP drop magnitude showed stronger associations than SBP drop magnitude, which might indicate that DBP plays a role to maintain a minimum level of cerebral perfusion. Cerebral autoregulation might potentially enhance cerebral perfusion dependent on the superposed pulse pressure (i.e. the difference between SBP and DPB), as suggested by a study reporting that pulse pressure was positively associated with cortical gray matter volume in patients with atherosclerotic disease while DBP was not.[32]

Delayed blood pressure drops

The strong association of SBP drop rate with number of falls in the 15 – 180-second interval indicates that rapid SBP drops occurring after 15 seconds after standing up are of special clinical relevance. This might be due to a decrease in patient alertness for fall risk (e.g. by lightheadedness) after 15 seconds if no symptoms occurred in the first 15 seconds, leading to lower tendency to use fall prevention strategies (e.g. leg muscle tensing, crossing the legs, holding a chair, etc.). However, this hypothesis needs to be tested in future research.

Fried criteria versus the four frailty markers

In the present study a modified version of the Fried criteria as well as the four frailty markers were used. The Fried criteria and the four frailty markers represent different constructs, the four frailty markers being more subjective than the Fried criteria. This was reflected by the different associations of the BP parameters with the two frailty criteria as DBP drop magnitude in the 15 – 180-second interval had the strongest association with frailty according to the Fried criteria and SBP drop rate in the 0 – 15-second interval had the strongest association with frailty according to the four frailty markers. This might indicate that short-term rapid BP drops are particularly related to the perception of orthostatic symptoms and therefore affect

subjectively assessed frailty components as mobility and activities of daily living. More persistent BP drops, on the other hand, might particularly affect more objective frailty components as gait speed and handgrip strength.

Strength and limitations

The strength of this study is that it systematically compares the clinical relevance of BP drop rate, BP drop magnitude and baroreflex sensitivity in a population of geriatric outpatients. Furthermore, it elucidates the value of continuous BP measurements, as these are necessary to compute BP drop rate, and BP drop magnitude in the 0-15 second interval. Limitations include the cross-sectional design of the study, limiting the conclusions that can be drawn about the causal nature of the relationship, and the use of subjectively measured number of falls. The BRS measure used in the present study did not discriminate between the effect of blood pressure drop and heart rate increase.

Perspectives

The results of this study advocate the use of continuous BP measurements in geriatric outpatients and identify BP drop rate as a clinically relevant parameter to assess in these patients. Potential future applications include the use of BP drop rate to predict frailty and falls related to orthostatic BP drop and to evaluate the efficacy of OH treatment.

Conclusion

BP drop rate after standing up is associated with frailty and number of falls in geriatric outpatients, and may reflect the imposed challenge to the baroreflex rather than BP drop magnitude. The results indicate that BP drop rate is particularly related to clinical outcome.

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Chapter 6

Orthostatic blood pressure recovery associates with physical performance, frailty and number of falls in geriatric outpatients

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Abstract

Objective: Blood pressure (BP) recovery after orthostatic hypotension (OH) might be important to prevent cerebral hypoperfusion episodes in older adults, and be related to better clinical outcome. The objective was to study the relationship between BP recovery and clinical outcome, i.e., physical and cognitive performance, frailty and falls, in geriatric outpatients.

Methods: 168 geriatric outpatients underwent continuous (beat-to-beat) BP measurements during standing up, and a comprehensive geriatric assessment, including assessment of physical performance (chair stand test), cognitive performance (Mini Mental State Examination), frailty (Fried criteria) and falls in the previous year. BP recovery was evaluated at 15-30, 30-60, 60-120 and 120-180 seconds after standing up and defined as mean systolic and diastolic BP in the respective time intervals minus baseline BP. Associations with clinical outcome were assessed using linear (physical and cognitive performance and frailty) and logistic (falls) regression, adjusting for age, sex, baseline BP and initial BP drop.

Results: Systolic BP recovery was associated with frailty (30-60 seconds interval; $\beta = 0.013$, $p = 0.02$) and falls (30-60 seconds interval; odds ratio = 1.024, $p = 0.02$). Diastolic BP recovery was associated with physical performance (30-60 seconds interval; $\beta = 0.215$, $p = 0.01$), frailty (30-60 seconds interval; $\beta = 0.028$, $p = 0.02$) and falls (30-60 seconds interval; odds ratio = 1.039, $p = 0.04$). Neither systolic nor diastolic BP recovery was associated with cognitive performance.

Conclusions: Diastolic BP recovery was particularly associated with clinical outcome in geriatric outpatients, suggesting BP recovery to be of clinical interest.

Introduction

Orthostatic hypotension (OH), defined as a sustained systolic blood pressure (BP) drop > 20 mmHg or a diastolic BP drop > 10 mmHg within three minutes after orthostasis, is a prevalent disease in older adults, associated with poor clinical outcome such as poor physical and cognitive performance, cardiovascular diseases, falls and mortality.[1–6] Brain hypoperfusion might act as a mediator in this relationship, potentially causing episodes of acute cerebral oxygen deficit directly after standing up and chronic brain lesions if these episodes are recurrent.[7–13] The adequacy of brain perfusion after standing up may be determined by BP recovery after the orthostatic BP drop, i.e., the difference between BP after standing up and baseline (i.e., supine) BP as a function of time.

Existing studies are inconclusive with respect to the association between BP recovery after OH and clinical outcome, partly due to the lack of consensus about BP recovery measures. BP recovery defined as the percentage of baseline BP that is recovered was found to be associated with mortality, only when assessed between

15-20 seconds after standing up.[14] Impaired BP recovery defined as a BP below the OH criteria at least at 60 – 110 seconds after standing, evaluated every ten seconds, was reported to be associated with falls.[15,16] The recovery of systolic BP at 30, 60 and 180 seconds after standing up was used in some studies to classify a patient into one of four BP recovery categories.[17–19] In some other studies, BP recovery patterns were clustered using a k-means algorithm, but no association with cognitive performance or comorbidity was found.[20,21] The different BP recovery measures have not been assessed systematically in the same population with respect to their association with clinical outcome. Furthermore, the role of baseline BP and initial BP drop (i.e., within 15 seconds after standing) in this association is unclear, though these might be determinants of BP recovery.[18]

This study in geriatric outpatients addressed a) the association between BP recovery measures (systolic and diastolic, assessed in subsequent time intervals) and clinical outcome, i.e. physical and cognitive performance, frailty and number of falls; b) the role of baseline BP and initial BP drop in the aforementioned association.

Methods

Study design and setting

Data from two cohorts of patients (Bronovo and COGA) were used. The Bronovo cohort included all patients referred to the geriatric outpatient clinic of the Bronovo hospital (The Hague, the Netherlands) between March 2011 and January 2012. The COGA cohort included all patients referred to the Center of Geriatrics in Amsterdam (COGA) of the VU University Medical Center Amsterdam (Amsterdam, the Netherlands) between January 2014 and December 2015. All patients underwent a comprehensive geriatric assessment (CGA). The studies were performed in accordance with the Declaration of Helsinki and approved by the local medical ethical committee of the VU University Medical Center Amsterdam (COGA cohort) and the institutional review board of the Leiden University Medical Centre (Bronovo cohort).

Patient characteristics

Age, sex, height, weight, medical history, medication, living situation, smoking habits and alcohol consumption were extracted from the medical records. Multi-morbidity was defined as two or more of the following diseases: chronic obstructive pulmonary disease, diabetes mellitus, hypertension, malignancy, myocardial infarction, Parkinson's disease, (osteo)arthritis.

Blood pressure measurement

A random selection of patients underwent continuous beat-to-beat BP measurements during standing up from supine to standing position. Continuous BP was measured

using a finger photoplethysmograph (Nexfin; BMEYE, Amsterdam, the Netherlands). Finger photoplethysmographic continuous BP monitors have been validated using intra-arterial BP measurements both during rest and orthostatic challenges.[22–24] Patients were asked to lie in a supine position for 5 minutes after which they were asked to stand up and continue standing for 3 minutes. The last minute of supine resting BP data was used as baseline. Standing up was supported by an automatic lift chair (Vario 570, Fitform B.V. Best, The Netherlands) in the Bronovo cohort. The time instance of standing up was marked in the data.

Blood pressure analysis

All BP signal analyses were performed using MATLAB R2017b (the Mathworks Inc., Natrick, MA). If signals were incomplete (baseline < 30 seconds or standing time < 150 seconds) or very noisy on inspection they were excluded. A 5-second window moving average filter was applied. Signals were split into three epochs based on the transition marker in the data indicating the moment of standing; resting (60 seconds), transition (7 seconds) and standing (180 seconds).

Baseline BP ($BP_{baseline}$) was defined as the mean of the 60-second resting epoch before transition. Initial BP drop ($BP_{initial\_drop}$) was defined as baseline minus the minimum BP in the 0-15 second interval; minimum BP (BP_{min}) as the lowest BP in this time interval.

BP recovery was evaluated for both systolic and diastolic BP in the following time intervals (ti) after standing up: 15-30, 30-60, 60-120 and 120-180 seconds. BP recovery was defined as follows, higher values indicating worse recovery.

$$BP_{recovery,ti} = BP_{baseline} - mean(BP_{ti})$$

Clinical outcome

Physical performance during standing up was assessed using the chair stand test. Patients were asked to stand up from sitting position (knees in 90 degrees flexion) and sit down five times as quickly as possible without the use of their arms or hands.[25] The time in seconds needed to complete this task was used for the analysis.

Cognitive performance was assessed using the Mini Mental State Examination (MMSE©, Par Inc, USA).[26] Subdomains assessed by the MMSE include orientation to time and place, attention, calculation, recall, language, repetition and complex commands.

Frailty was assessed using the Fried frailty criteria, which assess unintentional weight loss, exhaustion, physical inactivity, gait speed, and handgrip strength.[27] A patient can be frail on each of these items resulting in a frailty score with range 1-5. Weight loss was defined as a patient-reported loss of more than 3 kg in the previous month or more than 6 kg in the previous 6 months.[28] Exhaustion was assessed using the individual question ‘I feel as if I am slowed down’ answered

with 'very often' or 'nearly all the time' on the Hospital Anxiety and Depression Scale.[28,29] Physically inactive was defined as a patient-reported maximum distance of outdoor walking less than 20 minutes, only walking indoors, or not walking at all.[28] Gait speed was assessed using the 4-meter walk test.[28] Handgrip strength was defined as maximal force in kilograms of 3 performances on each hand, by using hand-held dynamometry (JAMAR hand dynamometer; Sammons Preston, Inc., Bolingbrook, IL).[28]

Self-reported number of falls was defined as how many times patients reported to have fallen in the past year.

Statistical analysis

The Statistical Package for the Social Science (IBM SPSS Statistics version 22, IBM Corporation, Chicago, IL) were used for statistical analysis. Normally distributed variables were reported using mean and standard deviation (SD); other variables using median and interquartile range (IQR).

The association between BP recovery and physical and cognitive performance frailty was assessed using linear regression analyses with BP recovery as independent variable and physical and cognitive performance as dependent variables. The association between BP recovery and number falls was assessed using logistic regression analyses with BP recovery as independent variable and number of falls as dependent variable, dichotomized by the group median. All analyses were adjusted for age and sex in model 1, and additionally adjusted for baseline BP in model 2 and additionally adjusted for initial pressure drop in model 3. All analyses were also performed with standardized (z-score) variables, to enable comparison between regression coefficients of the different clinical outcomes.

Results

Table 6.1 represents the characteristics of the 168 geriatric outpatients (109 and 59 patients from the COGA and Bronovo cohorts, respectively) included in the analyses. The mean age of patients was 81.4 years (SD = 7.0); 55.4% of the patients were female and 83.5% of patients were living at home. Mean SBP and DBP were 139 mmHg (SD = 28.8) and 70.8 mmHg (SD = 13.3), respectively.

Figure 6.1 shows the associations between BP recovery and physical performance, cognitive performance, frailty and number of falls. The data are provided in eTable 1(http://links.lww.com/HJH/B438) and the results from the standardized analysis are provided in eFigure 1 (http://links.lww.com/HJH/B438). After adjustments for baseline BP and initial BP drop, particularly diastolic BP recovery in the 30-60 second interval was associated with physical performance: beta 0.215 (95% confidence interval (CI) 0.05-0.38, p 0.01).

Both systolic and diastolic BP were particularly associated with frailty in the

Table 6.1. Patient characteristics

Characteristics	All N (%)		Bronovo N (%)		COGA N (%)	
Sociodemographic						
Age, years, mean (SD)	168 (100)	81.4 (7.2)	59	80.8 (7.1)	109	81.8 (7.2)
Gender female, n (%)	168 (100)	93 (55.4)	59	33 (56.0)	109	60 (55.0)
Living at home, n (%)	166 (98.8)	137 (82.5)	59	47 (79.7)	107	90 (84.1)
Health characteristics						
Currently smoking, n (%)	162 (96.4)	22 (13.6)	59	9 (15.3)	103	13 (12.6)
Excessive alcohol use, n (%)[a]	131 (78.0)	12 (9.2)	59	6 (10.2)	72	6 (8.3)
Multi-morbidity, n (%)[b]	161 (95.8)	70 (43.5)	57	20 (35.1)	104	50 (48.1)
BMI, kg/m^2, mean (SD)	163 (97.0)	25.9 (4.6)	58	26.3 (4.9)	105	25.7 (4.5)
No. of medications, median (IQR)	162 (96.4)	6.0 (4.0 - 6.0)	58	5.5 (3.8 – 7.3)	104	7 (4.0 – 9.0)
Supine resting blood pressure						
Systolic, mmHg, mean (SD)	168 (100)	138.1 (27.6)	59	148.2 (25.8)	109	13.7 (27.0)
Diastolic, mmHg, mean (SD)	168 (100)	70.6 (13.2)	59	72.1 (15.7)	109	68.6 (11.2)
Initial (0 - 15 seconds) blood pressure drop						
Systolic, mmHg, mean (SD)	168 (100)	27.6 (23.9)	59	14.2 (19.5)	109	18.3 (22.4)
Diastolic, mmHg, mean (SD)	168 (100)	13.2 (15.4)	59	6.5 (15.2)	109	6.3 (13.8)
Initial orthostatic hypotension, n (%)[c]	168 (100)	61 (36.3)	59	21 (35.6)	109	40 (36.7)
Blood pressure recovery (15 – 180 seconds)						
Systolic, 15-30 seconds, mean (SD)	168 (100)	10.2 (24.3)	59	8.4 (21.7)	109	11.2 (25.6)
Systolic, 30-60 seconds, mean (SD)	168 (100)	4.4 (23.6)	59	0.7 (21.7)	109	6.4 (26.0)
Systolic, 60-120 seconds, mean (SD)	168 (100)	-3.5 (26.1)	59	-9.2 (19.8)	109	-0.5 (28.6)
Systolic, 120-180 seconds, mean (SD)	168 (100)	-6.4 (29.0)	59	-12.2 (22.1)	109	-3.3 (31.8)
Diastolic, 15-30 seconds, mean (SD)	168 (100)	2.3 (15.7)	59	3.1 (17.8)	109	1.7 (14.5)
Diastolic, 30-60 seconds, mean (SD)	168 (100)	-1.3 (13.0)	59	-1.8 (14.7)	109	-1.0 (12.0)
Diastolic, 60-120 seconds, mean (SD)	168 (100)	-4.6 (11.5)	59	-6.0 (11.7)	109	-3.8 (11.4)
Diastolic, 120-180 seconds, mean (SD)	168 (100)	-5.4 (14.7)	59	-6.3 (11.8)	109	-5.0 (16.0)
Orthostatic hypotension, n (%)[d]	168 (100)	24 (14.3)	59	6 (10.2)	109	18 (16.5)
Clinical outcome						
Chair stand test, s, median (IQR)	133 (79.2)	13.9 (11.3 – 18.7)	52	14.2 (11.6 – 19.8)	81	13.7 (10.9 – 17.8)

MMSE, median (IQR)	159 (94.6)	27.0 (24.0 - 29.0)	59	27.0 (25.0 –29.0)	100	26.0 (23.0 – 28.0)
Fried frailty score, mean (SD)	130 (77.4)	1.92 (1.3)	59	1.46 (1.2)	71	1.98 (1.2)
Number of Falls, median (IQR)	145 (86.3)	1 (0 – 3)	53	1 (0 – 2)	92	2 (0 – 3)

BMI , body mass index; BP, blood pressure; IQR, interquartile range; MMSE, Mini-Mental State Examination; OH, orthostatic hypotension; OH, prevalence of OH assessed using continuous BP measurements; SBP, systolic blood pressure; ADL, Activities of daily living. [a]Excessive alcohol use is defined as >14 units per week for women and >21 units per week for men. [b]Multimorbidity is defined as ≥ 2 diseases of the following: chronic obstructive pulmonary disease, diabetes mellitus, hypertension, malignancy, myocardial infarction, Parkinson disease, or rheumatoid/(osteo)arthritis. [c]Initial orthostatic hypotension is defined as a systolic blood pressure drop > 40 mmHg and/or a diastolic blood pressure drop > 20 mmHg within 15 seconds after standing up. [c]Initial orthostatic hypotension is defined as a systolic blood pressure drop > 40 mmHg and/or a diastolic blood pressure drop > 20 mmHg within 15 seconds after standing up. [d]Orthostatic hypotension is defined as a sustained systolic blood pressure drop > 20 mmHg and/or a diastolic blood pressure drop > 10 mmHg occurring within 3 minutes after standing up.

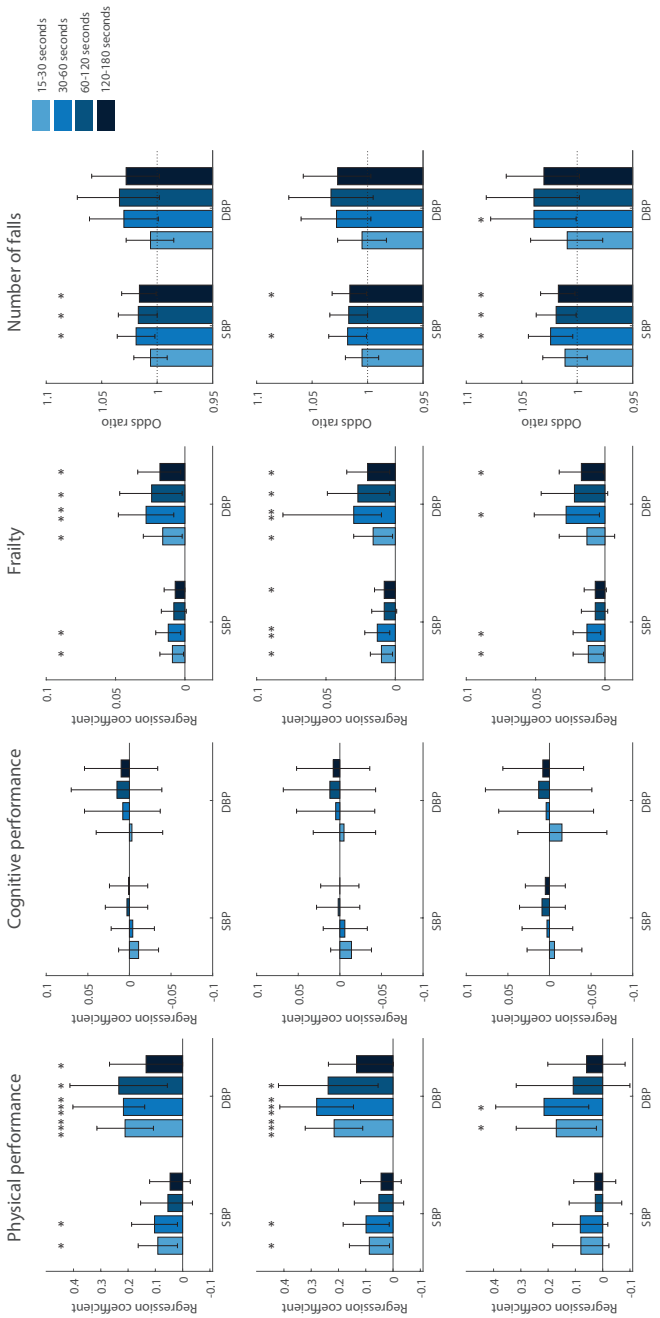

Figure 6.1. Blood pressure recovery and clinical outcome. The bars indicate the regression coefficients / odds ratios of the regression analyses between blood pressure recovery and clinical outcome. Clinical outcome is represented by physical performance (i.e. time in seconds needed for the chair stand test, n = 133), cognitive performance (i.e. score on Mini Mental State Examination, n = 159), frailty (i.e. number of frailty items using the Fried criteria, n = 130) and self-reported number of falls in the past year (n = 145). Model 1 adjusts for age and sex, model 2 additionally adjusts for baseline blood pressure and model 3 additionally adjusts for the initial blood pressure drop. The error bars indicate the 95% confidence interval. Stars indicate statistical significance, one, two and three stars denoting $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively. SBP: systolic blood pressure; DBP: diastolic blood pressure.

30-60 second interval. Adjustment for both baseline BP and initial BP drop had only minor effect on the strength of these associations. The regression coefficients were 0.013 for systolic BP (95% CI 0.00 – 0.02, p 0.02) and 0.028 for diastolic BP (95% CI 0.00 – 0.05, p 0.02), after full adjustment.

After full adjustment, diastolic BP recovery assessed in the 30-60 second interval was particularly associated with the number of falls (odds ratio 1.039, 95% CI 1.00 – 1.08, p 0.04).

None of the BP recovery measures was associated with cognitive performance.

Discussion

In a cohort of 168 geriatric outpatients, BP recovery after orthostatic hypotension was significantly associated with physical performance, assessed using the chair stand test, frailty according to the Fried criteria and self-reported number of falls, but not with cognitive performance. Diastolic BP recovery assessed in the 30-60 second interval was particularly associated with clinical outcome. Adjusting the association between BP recovery and clinical outcome for baseline BP and initial BP drop had only minor effect on the strengths of the associations.

The association between BP recovery and number of falls found in the present study as well as the absence of any association between BP recovery and cognitive performance is in line with results from previous studies.[15,16,20,21] However, a recent study reported an association between BP recovery and cognitive decline and mortality in patients with Alzheimer's Disease.[30] This may be due to the fact that patients with Alzheimer's disease have increased vulnerability for cognitive decline compared to the population of the present study. The study in patients with Alzheimer's disease also reported diastolic BP recovery assessed at 1 minute after postural change to be particularly associated with clinical outcome, which is in line with the findings of the present study.[30]

Mechanisms underlying the found associations

The results might indicate that adequate BP recovery after orthostasis may potentially prevent episodes of brain oxygen deficit and thereby improve clinical outcome, as suggested by previous studies reporting hypotensive episodes to be associated with brain white matter hyperintensities and cortical atrophy.[7–11,31,32] However, no conclusions on the causality of the found associations or the involved mechanism can be inferred from the results and orthostatic symptoms suggesting cerebral hypoperfusion are only weakly associated with orthostatic hypotension.[33]

Confounding due to degenerative processes causing both worse BP recovery poor clinical outcome might explain part of the results found in the present study. Calf muscle deconditioning may lead to impaired BP recovery as it has a role in the maintenance of adequate venous return and BP, which may start within seconds

after standing up.[34,35] Calf muscle deconditioning may also negatively affect physical performance and increase frailty.

The absence of an association between BP recovery and cognitive performance is remarkable considering the results of a recent meta-analysis, which reported an association between OH and cognition.[4] These differences may be explained by differences in measurement method (sphygmomanometer BP measurements versus continuous BP measurements) or assessed time interval (initial BP drop within 15 seconds after standing up versus BP recovery after 15 seconds after standing up). Furthermore, the relatively high cognitive performance of the overall cohort in the present study may potentially have caused a ceiling effect. Differences may also be partly due to the fact that results reported in the present study were corrected for age while the results from most studies included in the meta-analysis results were not.

Relative strengths of the associations

The particularly strong association between diastolic BP and clinical outcome may be explained by the large contribution of diastolic BP to cerebral perfusion pressure: cerebral perfusion pressure is defined as mean arterial pressure minus intracranial pressure;[36] mean arterial pressure is a weighted average of systolic (single weight) and diastolic (double weight) BP; in the context of a constant intracranial pressure, changes in diastolic BP have twice as large an effect on cerebral perfusion pressure.[37]

Overall, BP recovery was particularly associated with clinical outcome in the 30-60 second interval. Explanations remain hypothetical, but could be sought in the brain tolerance for hypoperfusion, i.e., the time delay between when brain hypoperfusion starts and the first neurobiological consequences. The relatively weaker association in the 120-180 second interval with clinical outcome might indicate a compensation mechanism may play a role, though its nature is uncertain. Near-infrared spectroscopy measurements (NIRS) should be performed in future studies to quantify the brain oxygen concentration levels in the different time intervals and relate these to clinical outcome.[38–40]

Role of baseline blood pressure and initial blood pressure drop

Adjustment for baseline BP had overall minor effect on the strength of the associations, which may indicate that an individual's physiological regulatory systems (i.e. cerebral autoregulation and baroreflex sensitivity) are adapted to their baseline BP. This would for example imply that a diastolic BP recovery value of 30 mmHg would be an equal challenge for individuals with baseline diastolic BP of 100 and 60 mmHg. Adjustment for initial BP drop overall slightly attenuated the strengths of the association between BP recovery and physical performance and frailty, indicating that BP recovery should always be considered in the context of the initial BP drop.

BP recovery versus BP drop

BP drop and recovery have different mechanisms which cannot be easily disentangled from BP alone. BP drops typically occur due to pooling of blood in the legs caused by gravitational forces within 15 seconds after standing up.[18] However, venous pooling after standing up may be prolonged,[6,41] implying that the BP recovery measures used in the present study may partly reflect this prolonged venous pooling. These BP recovery measures therefore reflect the net BP resulting from BP lowering gravitational forces and BP increasing recovery mechanisms such as arterial and venous contraction, heart rate and contractility increase and (calf) muscle activation.[34,42–44] The relative contribution of gravitational forces and the recovery mechanisms to BP varies over time after standing up, and also differs between individuals, complicating the distinction of these mechanisms based on BP measurements alone.[6,45] How recovery mechanisms react to BP drops and how to measure the capacity of the system to recover from BP shifts after postural transitions needs to be further investigated in further studies. These studies should address venous pooling, calf muscle use, heart rate, cardiac contractility and arterial vasoconstriction.

Strength and limitations

The strength of this study is the systematic assessment of BP recovery measures suggested in the literature with regard to their clinical relevance. Limitations include the cross-sectional design of the study, precluding conclusions about causality, the absence of measurements potentially indicative for the pathophysiological mechanisms involved (e.g. NIRS), the subjective assessment of the number of falls and the relatively high cognitive performance in the investigated group, which may have caused a ceiling effect in the analyses.

Conclusion

BP recovery was associated with physical performance, frailty and number of falls, but not with cognitive performance. Baseline BP and initial BP drop only played a minor role in this association. The results suggest BP recovery, particularly diastolic BP recovery in the 30-60 second interval, to be clinically important. The results further suggest the use of continuous BP measurements for assessment of BP recovery in patients with orthostatic hypotension.

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Part III

Baroreflex sensitivity, peripheral vasoconstriction, cerebral oxygenation and autoregulation derived from PPG, ECG and NIRS measurements

Chapter 7

Sensitivity and reliability of cerebral oxygenation responses to postural changes measured with near-infrared spectroscopy

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Abstract

Purpose: Cerebral oxygenation as measured by near-infrared spectroscopy (NIRS) might be useful to discriminate between physiological and pathological responses after standing up in individuals with orthostatic hypotension. This study addressed the physiological sensitivity of the cerebral oxygenation responses as measured by NIRS to different types and speeds of postural changes in healthy adults and assessed the reliability of these responses.

Methods: Cerebral oxygenated hemoglobin (O_2Hb), deoxygenated hemoglobin (HHb) and tissue saturation index (TSI) were measured bilaterally on the forehead of 15 healthy individuals (12 male, age range 18-27) using NIRS. Participants performed three repeats of sit to stand, and slow and rapid supine to stand movements. Responses were defined as the difference between mean, minimum and maximum O_2Hb, HHb and TSI values after standing up and baseline. Test-retest, inter observer and inter sensor reliability were addressed using intraclass correlation coefficients (ICCs).

Results: The minimum O_2Hb response was most sensitive to postural changes and showed significant differences (-4.09 µmol/L, $p < 0.001$) between standing up from sitting and supine position, but not between standing up at different speeds (-0.31 µmol/L, $p = 0.70$). The minimum O_2Hb response was the most reliable parameter (ICC > 0.6).

Conclusions: In healthy individuals, NIRS based cerebral oxygenation parameters are sensitive to postural change and discriminate between standing up from supine and sitting position with minimum O_2Hb response as the most sensitive and reliable parameter. The results underpin the potential value for future clinical use of NIRS in individuals with orthostatic hypotension.

Introduction

Adequate cerebral oxygenation is essential for physical and cognitive functioning.[1–4] Cerebral oxygenation depends on blood pressure and cerebral perfusion,[5] which are challenged by postural changes, such as standing up from supine or sitting position.[6] Changes in blood pressure and cerebral perfusion after standing up are counteracted by the baroreflex and cerebral autoregulation.[7,8] However, these systems do not fully prevent cerebral oxygenation drops after standing up in most individuals,[9] which may be the cause of symptoms of dizziness, impaired physical function and falls in patients with impaired blood pressure control after standing up, i.e., orthostatic hypotension.[10–12]

To discriminate between physiological and pathological cerebral oxygenation responses, physiological responses to various types and speeds of postural changes must be investigated. Near-infrared spectroscopy (NIRS) is a non-invasive

and non-obtrusive method to measure cerebral oxygenation and was suggested to be valid by studies reporting the correlation of NIRS signals with fMRI BOLD signals and cerebral blood flow measured by transcranial Doppler.[13,14] Furthermore, NIRS is potentially useful to assess cerebral autoregulation.[15,16] Previous studies investigated cerebral oxygenation responses using NIRS in healthy adults during head up tilt,[5,17,18] compared responses to standing up or sitting up in younger and older adults,[6,19–21] compared responses to standing up with and without calf muscle tensing, [9,20] or determined reproducibility of responses in older adults.[22] These studies reported a cerebral oxygenation drop within 30 seconds after standing up. However, a comprehensive assessment of the dependence of NIRS derived cerebral oxygenation responses on the type (i.e. standing up from supine versus sitting position) and speed of postural change (i.e. slow versus rapid standing up) is missing and the reliability of these responses have not been assessed.

This aim of this study was to investigate sensitivity of the cerebral oxygenation response as measured by NIRS to different types and speeds of postural changes in healthy adults and to assess the reliability of these responses.

Methods

All data generated or analyzed during this study are included in the supplementary information file of the published article**.**

Subjects

Fifteen healthy young (mean age 22 years, SD 2.8; twelve male) individuals were recruited via oral and written advertisement in an undergraduate university teaching setting.

Volunteers were excluded from participation when: having a history of stroke, cardiovascular- or cerebrovascular diseases, cardiac arrhythmias, cardiovascular related medication use, diabetes mellitus or orthostatic hypotension. Exclusion criteria were checked prior to study participation by completing a short survey. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the Faculty of Science of the Radboud University in Nijmegen. Informed consent was obtained from all individual participants included in the study.

Instrumentation

NIRS signals reflecting concentration changes of cerebral oxygenated hemoglobin (O_2Hb) and deoxygenated hemoglobin (HHb) and cerebral tissue saturation index (TSI) were continuously measured bilaterally on the forehead, approximately 2.5 cm

above the eyebrows, using two Portalite systems (Artinis Medical Systems B.V., Elst, The Netherlands), each consisting of three light sources and one detector. The inter optode distance (i.e. the distance between the light sources and the light detector) of the different light sources was 30, 35 and 40 mm. The sampling frequency was set at 50 Hz. O_2Hb and HHb were computed using the modified Lambert-Beer law using Oxysoft (version 3.0, Artinis Medical Systems B.V., Elst, The Netherlands), calculating the differential pathway using the formula proposed by Scholkman et al.[23,24] TSI, defined as oxygenated hemoglobin as a percentage of total hemoglobin, was computed using spatially resolved spectroscopy.[25]

To identify the start of postural change, a digital goniometer was attached to the participant's trunk to measure its angle relative to the horizontal. Time needed to stand up was defined as the time from the beginning of the first deviation from baseline to the instance where the angle was stabilized.

Beat-to-beat mean arterial pressure, inter beat interval and cardiac output were measured to assess whether cerebral oxygenation responses to postural changes correspond to systemic cardiovascular responses, as these are considered to be a cause of cerebral oxygenation drops.[26] Mean arterial pressure, inter beat interval and cardiac output were measured continuously using a photoplethysmograph with a cuff placed on the left middle finger (Finapres NOVA, Finapres Medical Systems BV, Enschede, The Netherlands). Peripheral oxygen saturation (SpO_2) was measured to assess blood oxygenation changes during standing up. An analogue reference signal containing a binary coding of time was imported in every device to enable off-line synchronization of the signals.

Protocol

The measurements were performed in a quiet, semi dark room with a room temperature of 21-23° Celsius. Three different postural changes were performed, after demonstration of the correct task execution using a short video: 1) sit to stand, defined as standing up from sitting position at a self-chosen speed; 2) slow supine to stand, defined as standing up from supine position in approximately 10 seconds; 3) rapid supine to stand, defined as standing up from supine position within 3 seconds.

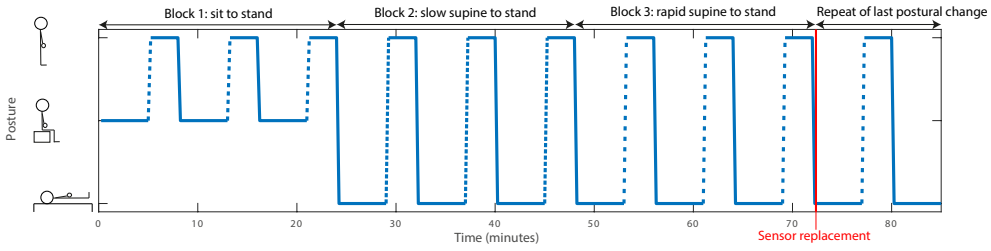

Figure 7.1. Protocol of postural changes. The sequence of the three blocks varied among subjects due to block randomization. Each block consists of three repeats. The empty space between the dashes indicates the speed of standing up, more space indicating higher speed.

Subjects were stimulated to relax, instructed not to talk and asked to move as little as possible during the experiment. The three different postural changes were performed in blocks, consisting of three repetitions per block. Each repetition encompassed a 5-minute resting period (supine or sitting) and a 3-minute standing period (Figure 7.1). The sequence of the blocks was randomized among participants to eliminate bias due to previous postural changes. After the three blocks, the NIRS system was reapplied by a second investigator to assess inter observer reliability. Then the last performed postural change was repeated once.

Data analysis

NIRS, goniometer and continuous blood pressure data were synchronized and analyzed off line using MATLAB R2017b (MathWorks, Natick, United States). NIRS and mean arterial pressrue signals were filtered using a 5-second moving average filter to reduce artefacts. Baseline values of the signals were computed as means of the 60-second period before postural change. For visualization, all signals were normalized at baseline and signals from the left and right NIRS systems were averaged. Based on previous studies reporting an early and a late oxygenation drop, the period after standing up was divided into an early and late interval, i.e. 0 - 30 and 30-180 seconds after standing up, respectively.[6,11] Parameters expressing the mean, maximum and minimum were determined for each postural change and NIRS signal for both intervals. Signal response sensitivity for postural changes was defined as the difference between these parameters and baseline.

Statistical analysis

Statistical analyses were performed using the MATLAB R2017b statistics toolbox. Response differences between postural changes were tested using paired t-tests. The test-retest reliability (i.e. the agreement of responses between repeats), inter

Table 7.1. Characteristics of the cohort

Characteristic	All (n = 15)
Age, years, mean (SD)	22 (2.8)
Male, n (%)	12 (80)
Light skin colour, n (%)	13 (87)
Height, m, mean (SD)	1.80 (9.4)
Weight, kg, mean (SD)	71 (5.7)
Current smoking, n (%)	1 (6.7)
Excessive alcohol use, n (%)[a]	0 (0)
Resting HR, bpm, mean (SD)	75 (13)
Resting SBP, mmHg, mean (SD)	127 (7)
Resting DBP, mmHg, mean (SD)	74 (10)
Time needed for sit to stand, s, mean (SD)	4.3 (1.1)
Time needed for slow supine to stand, s, mean (SD)	14.4 (3.9)
Time needed for rapid supine to stand, s, mean (SD)	6.0 (1.5)

HR was computed as the baseline mean. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a sphygmomanometer. SD: standard deviation; BMI: Body Mass Index; HR: Heart rate; bpm: beats per minute; [a] Excessive alcohol use is defined as > 14 units per week for females and > 21 units per week for males.

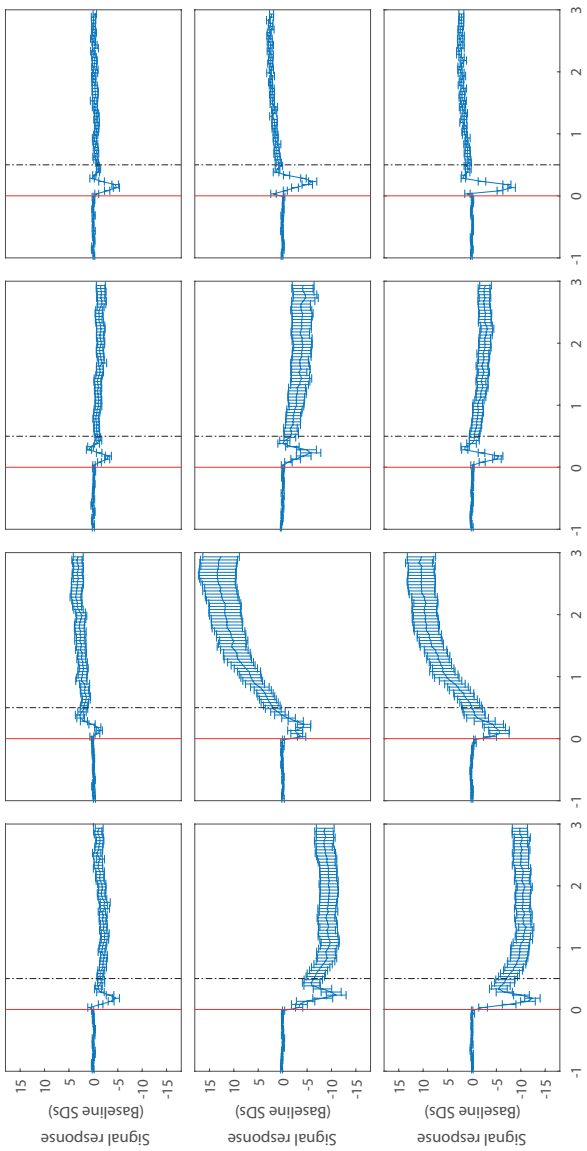

Figure 7.2. O_2Hb, HHb, TSI and mean arterial pressure before, during and after standing up as a response to different postural changes, averaged over subjects (n=15). All signals are unfiltered and normalized at baseline. The red vertical line indicates the onset of the postural change. The dashed line indicates the transition from the early (0 – 30 seconds) to the late (30 – 180 seconds) interval. The error bars indicate the standardized error of the mean.

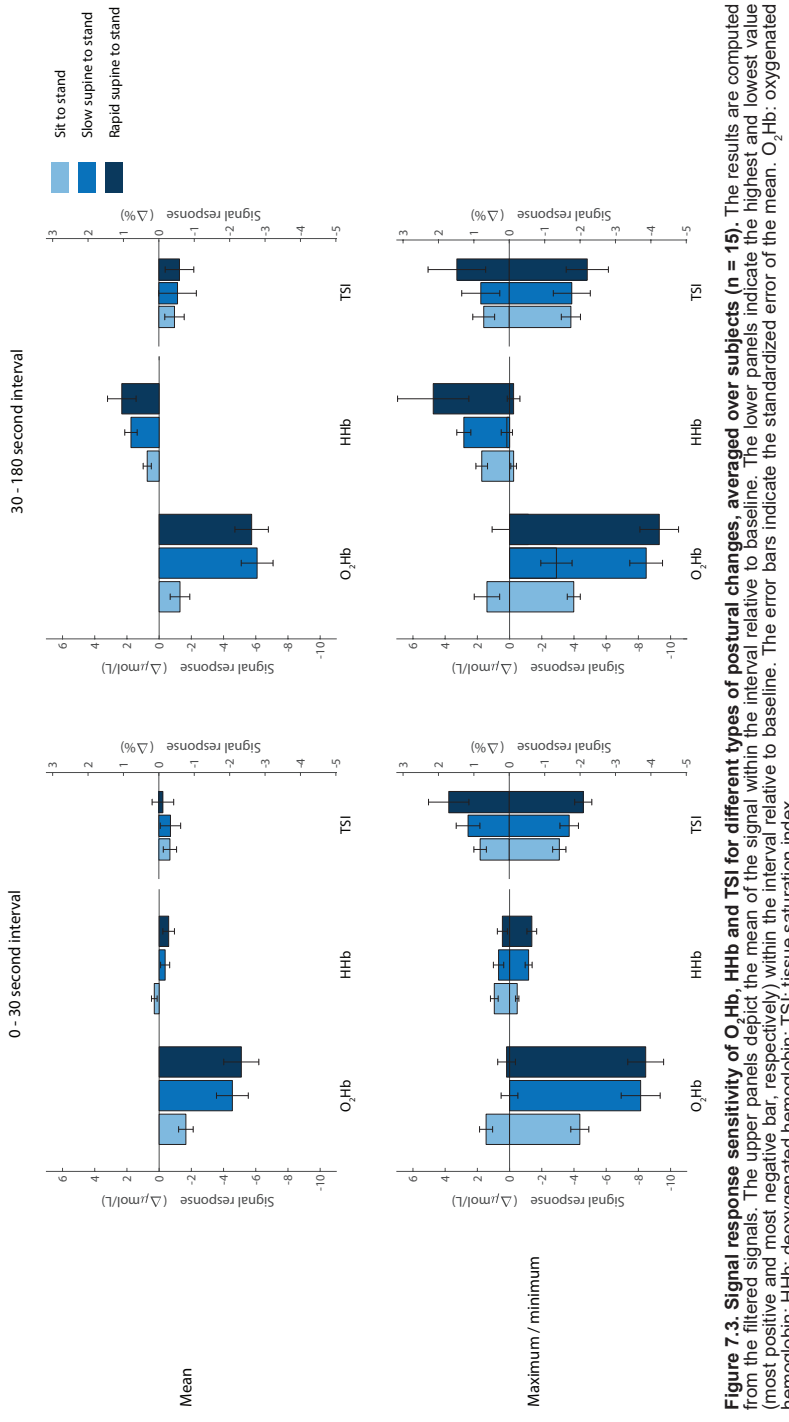

Figure 7.3. Signal response sensitivity of O_2Hb, HHb and TSI for different types of postural changes, averaged over subjects (n = 15). The results are computed from the filtered signals. The upper panels depict the mean of the signal within the interval relative to baseline. The lower panels indicate the highest and lowest value (most positive and most negative bar, respectively) within the interval relative to baseline. The error bars indicate the standardized error of the mean. O_2Hb: oxygenated hemoglobin; HHb: deoxygenated hemoglobin; TSI: tissue saturation index.

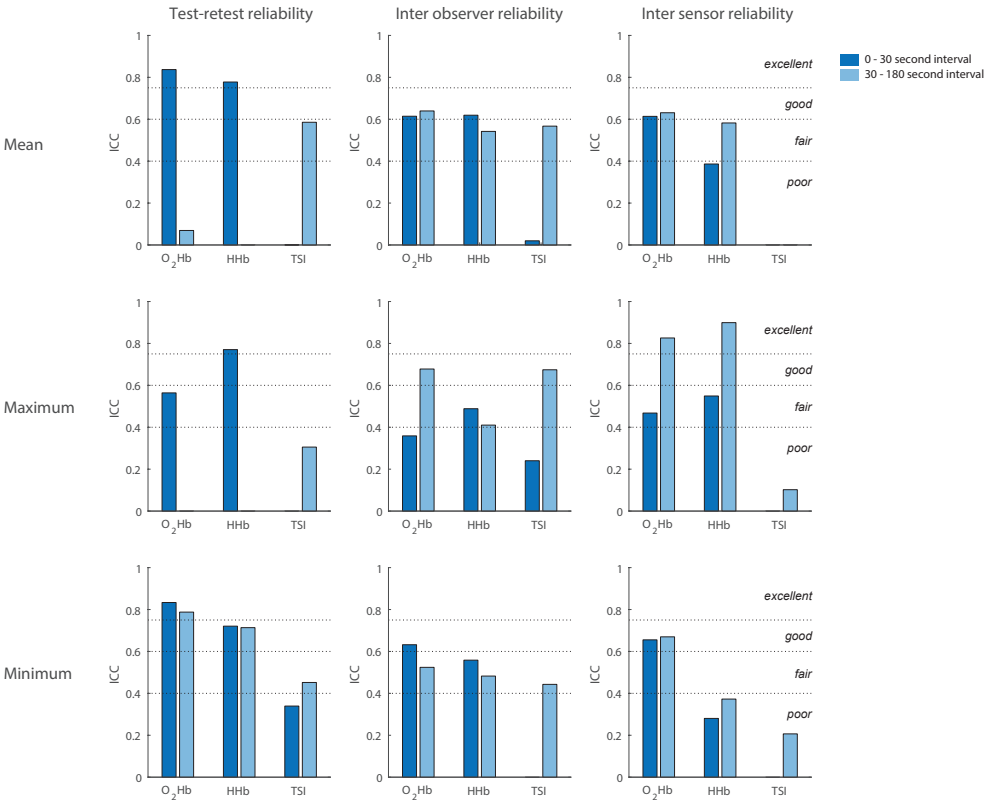

Figure 7.4. Test-retest reliability, inter observer reliability and inter sensor reliability, presented as intra class correlation (ICC), separate for each signal, response type and interval. The ICCs are computed from the filtered signals. The dotted lines delineate ICC scores regarded as excellent, good, fair and poor, as indicated in the right panels. An absent bar signifies an ICC of zero or lower. O_2Hb: oxygenated hemoglobin; HHb: deoxygenated hemoglobin; TSI: tissue saturation index.

observer reliability (i.e. agreement between responses before and after reapplication of the NIRS system) and inter sensor reliability (i.e. agreement between responses as measured simultaneously by left and right NIRS system) were expressed using one-way, random, single score intraclass correlation coefficients (ICCs),[27] and evaluated for each signal (i.e. O_2Hb, HHb and TSI), response type (i.e. mean, maximum and minimum) and interval (i.e. 0 – 30 seconds and 30 – 180 seconds). ICC scores between 0 – 0.40, 0.40 – 0.59, 0.60 – 0.74 and 0.75 – 1 were regarded as poor, fair, good and excellent, respectively.[28]

P-values below 0.05 were considered significant. Correction for multiple comparisons was performed according to the Bonferroni method, rendering p-values below 0.0009 significant.

Results

The characteristics of the included individuals are listed in table 7.1. Postural changes for sit to stand, slow supine to stand and rapid supine to stand were performed in 4.3 (SD 1.1), 14.4 (SD 3.9) and 6.0 (SD 1.5) seconds, respectively.

Figure 7.2 shows O_2Hb, HHb, TSI and mean arterial pressure before, during and after the three types of postural change (i.e. sit to stand, slow supine to stand and rapid supine to stand), normalized at baseline and averaged over all 15 subjects. In the early interval (0 – 30 seconds), O_2Hb, HHb and TSI showed a drop, which was most prominent in the O_2Hb signal and in the rapid supine to stand condition. In the late interval, O_2Hb and TSI showed a small decrease, while HHb showed a clear increase. None of the NIRS signals returned to baseline within the measurement period. Mean arterial pressure showed a pattern similar to O_2Hb and TSI in the early interval, but remained stable in the late interval. Supplementary figure S7.1 shows the cerebral oxygenation responses for the three female participants, showing similar patterns as the responses of the entire population.

Mean SpO_2 in the early interval did not differ significantly from baseline in any type of postural change. Inter beat interval and cardiac output showed a decrease and an increase in the early interval, respectively, for any postural change, as shown in Supplementary figure S7.2.

Figure 7.3 shows the O_2Hb, HHb and TSI signal response sensitivity to three postural changes for both intervals. As shown in Table 7.2, the responses differed significantly between sit to stand and both slow or rapid supine to stand, but no significantly different responses between slow and rapid supine to stand were observed. After correction for multiple comparisons, only differences in O_2Hb responses remained significant, both in the early and late interval. The largest mean arterial pressure drop after standing up was 24.0 (SD 9.8), 26.4 (SD 14.6) and 29.0 (SD 7.1) mmHg for sit to stand, slow supine to stand and rapid supine to stand, respectively, being not significantly different between conditions.

Figure 7.4 shows the test-retest reliability, inter observer reliability and inter sensor reliability for each signal, parameter and interval. Overall, the minimum O_2Hb response in the early interval resulted in the highest reliability scores, being good to excellent. None of the parameters derived from HHb and TSI had good or excellent test-retest, inter observer and inter sensor reliability.

Discussion

Cerebral oxygenation as measured by NIRS was sensitive to postural changes in healthy adults. Oxygenated hemoglobin (O_2Hb) showed the most prominent drop after standing up, which was significantly different between standing up from supine and from sitting position, but not between slow and rapid standing up. Compared to other parameters, the minimum O_2Hb response in the early interval showed good to

excellent reliability, identifying this as the preferred parameter in the assessment of cerebral oxygenation responses to postural changes.

Both oxygenated and deoxygenated hemoglobin dropped in the early phase after standing up, indicating a lower concentration of total hemoglobin, therewith reflecting a decrease of cerebral perfusion. This is in line with the early perfusion drop after standing up reported by transcranial Doppler studies.[9,11] This perfusion drop indicates cerebral autoregulation may not immediately compensate for blood pressure drops resulting from gravitational pooling after standing up, even in healthy adults.[8,29–31] The perfusion drop in the context of a constant brain oxygen demand is likely to be the cause of the cerebral hemoglobin saturation decrease, as reflected by the drop in TSI. Altered lung function during standing up may have contributed to the early drop in O_2Hb and TSI after standing up. However, SpO_2 did not show a significant drop after standing up, indicating this contribution was probably not large, if at all present. Furthermore, the decrease of inter beat interval decreased and

Table 7.2. NIRS response differences between postural changes.

	Sit to stand versus slow supine to stand	p-value	Sit to stand versus rapid supine to stand	p-value	Slow supine to stand versus rapid supine to stand	p-value
0 – 30 second interval						
O_2Hb, Δμmol/L, mean (SD)						
Mean	-2.89 (3.60)	0.0077*	-3.44 (3.64)	0.0026*	-0.56 (2.58)	0.4169
Max	-1.45 (2.44)	0.0368*	-1.27 (1.86)	0.0189*	0.18 (1.54)	0.6551
Min	-3.78 (3.82)	0.0018*	-4.09 (3.58)	0.0006**	-0.31 (3.04)	0.6959
HHb, Δμmol/L, mean (SD)						
Mean	-0.67 (1.06)	0.0279*	-0.89 (1.26)	0.0158*	-0.22 (0.99)	0.4047
Max	-0.27 (1.00)	0.3231	-0.50 (0.97)	0.0642	-0.24 (0.50)	0.0848
Min	-0.71 (0.98)	0.0143*	-0.91 (1.24)	0.0131*	-0.20 (1.05)	0.4689
TSI, Δ%, mean (SD)						
Mean	0.0 (1.1)	0.9580	0.2 (1.5)	0.6058	0.2 (1.4)	0.5495
Max	0.3 (1.2)	0.3031	0.9 (2.4)	0.1792	0.6 (2.4)	0.3941
Min	-0.3 (1.0)	0.3169	-0.7 (1.1)	0.0309*	-0.4 (0.8)	0.0625
30 – 180 second interval						
O_2Hb, Δμmol/L, mean (SD)						
Mean	-4.79 (3.78)	0.0002**	-4.45 (3.84)	0.0005**	0.34 (3.95)	0.7451
Max	-4.31 (3.71)	0.0005**	-2.57 (8.74)	0.2739	1.74 (8.59)	0.4448
Min	-4.50 (4.01)	0.0007**	-5.31 (4.44)	0.0004**	-0.81 (3.46)	0.3792
HHb, Δμmol/L, mean (SD)						
Mean	1.01 (1.10)	0.0031*	1.58 (3.06)	0.0663	0.57 (2.51)	0.3941
Max	1.11 (1.11)	0.0017*	3.01 (8.13)	0.1731	1.90 (7.67)	0.3537
Min	0.42 (1.41)	0.2653	0.00 (1.65)	0.9956	-0.42 (1.25)	0.2145
TSI, Δ%, mean (SD)						
Mean	-0.1 (2.1)	0.8743	-0.1 (1.9)	0.7806	-0.1 (1.0)	0.8259
Max	0.1 (1.9)	0.8672	0.8 (3.6)	0.4273	0.7 (3.5)	0.4644
Min	-0.0 (2.1)	0.9637	-0.5 (2.4)	0.4707	-0.4 (1.3)	0.2260

NIRS responses (i.e. mean, highest value and lowest value) in two intervals, compared between postural changes. Significantly different responses were observed when comparing sit to stand with supine to stand. The responses do not differ significantly between slow and rapid supine to stand. *statistically significant. **significant after correction for multiple comparisons

increase of cardiac output suggest a sufficient cardiac response to postural change, implying cardiac function does not account for the cerebral oxygenation drop.

The late, gradual drop of O_2Hb and TSI to below baseline and rise of HHb to above baseline are consistent with previous studies,[5,6,22] and are not likely to arise from gravitational pooling, as healthy adults usually recover blood pressure within 30 seconds after standing up.[29] These may be explained by a persistently decreased brain perfusion after standing up due to persistent hydrostatic pressure differences, as reported by transcranial Doppler studies.[6,9] The lower brain perfusion and a constant brain oxygen demand might cause a larger part of the available hemoglobin to become deoxygenated, thereby explaining a drop of O_2Hb and TSI and a rise of HHb.

The significantly different O_2Hb responses between standing up from sitting and supine position measured in the present study could not be explained by corresponding differences in blood pressure drop. Instead, these O_2Hb response differences might be explained by dependence of cerebral autoregulation on the type of postural change, independent of the magnitude of the blood pressure drop. The vestibular system may be involved, as standing up from supine and sitting position cause different vestibular stimuli, influencing cerebral autoregulation[32] and therewith cerebral oxygenation.

No significant differences were found between responses to rapid and slow supine to standing in the O_2Hb, HHb and TSI signals, as would be expected from studies showing that cerebral autoregulation acts as a high-pass filter, implying that rapid blood pressure drops cannot be compensated for as adequately as slow blood pressure drops.[33,34] Cerebral autoregulation may not have been tested to its maximum as measured differences of blood pressure drops between the slow and rapid supine to stand conditions in the present population were small and not significant. Further studies in patients with impaired blood pressure control, e.g. patients with orthostatic hypotension are required.

The lower overall test-retest reliability and inter sensor reliability of TSI responses compared to O_2Hb and HHb responses may be explained by an insufficient validity of the assumptions needed to compute TSI, such as homogeneity of brain tissue.[35,36] The substantial TSI response differences as measured by the left and right NIRS devices suggests different tissue properties underlying both devices, e.g. differences in skull thickness, which were reported to be considerable in a recent study.[37] Alternatively, a relatively low sensitivity of TSI to postural changes may imply that TSI parameters are relatively sensitive to noise, leading to lower TSI reliability scores.

The NIRS measurements investigated in the present study are potentially influenced by changes in scalp perfusion after standing up, which is not directly regulated by cerebral autoregulation. Studies on the contribution of scalp perfusion to cerebral oxygenation as measured by NIRS are contradictory. Cerebral oxygenation

was reported to correlate significantly with jugular vein oxygenation, but not with facial vein oxygenation, suggesting signals derived from NIRS measurements primarily reflect cerebral processes.[35] However, significant changes in TSI, as measured by NIRS were reported after inducing scalp ischemia using a tourniquet, indicating a significant influence of scalp blood flow.[38] The subjects needed more time to stand up than instructed in both the slow and rapid supine to stand conditions. This may be attributable to underestimation of the speed of standing up by the subjects. Alternatively, it may be due to the definition of the time needed to stand up, which requires a stabilized goniometer signal. If subjects stood up sufficiently rapid, but needed some extra time to fully stabilize, this may have prolonged the measured time needed to stand up.

Strength and limitations

The strength of this study is that it addresses the sensitivity of cerebral oxygenation signals for different types and speeds of postural change and systematically assesses the test-retest, inter observer and inter sensor reliability for various parameters. The small number of included individuals is a limitation of this study, potentially introducing sampling error and limiting study power. The majority of the included individuals were young males, potentially limiting generalizability. Furthermore, as the experiment included only one session, no conclusions can be drawn regarding the day-to-day reproducibility of the parameters, which may be important to explain the variation of cerebral oxygenation responses in healthy adults.

The results elucidate the cerebral oxygenation response to different types and speeds of postural change in healthy adults. However, they do not provide an integrative view on the cardiovascular reaction to postural change, which would contribute to the understanding of the pathophysiology of orthostatic hypotension. Future studies should address this issue, simultaneously assessing blood pressure, arterial and venous vasoreactivity, calf muscle function, sympathetic and parasympathetic function as well as cerebral oxygenation.

This study does not provide results on how to predict syncope or orthostatic symptoms, as these were not recorded in this study. However, the reported results on cerebral oxygenation changes during different types and speeds of standing up in healthy adults are necessary to determine any dependence of these responses on age in future studies and to classify future NIRS measurements in patients with orthostatic hypotension as physiological or pathological.

Conclusion and future direction

This study demonstrates that cerebral oxygenation responses measured using NIRS are sensitive to postural change and discriminate between standing up from supine and from sitting position, but not between slow and rapid standing up in healthy

adults. Furthermore, it identifies minimum O_2Hb response in the early interval as a sensitive and reliable parameter, suggesting this parameter to be of potential value for future clinical use in older adults with impaired blood pressure control, e.g. orthostatic hypotension. Future research should address other cardiovascular responses to postural change such as arterial and venous vasoreactivity in an integrative approach. Furthermore, it should address the effect of ageing on the cerebral oxygenation response to different types and speeds of postural change, and investigate the potential of NIRS to predict clinical outcomes such as falls in patients with orthostatic hypotension. In contrast to healthy adults, the speed of standing up might be important for the cerebral oxygenation response in this group of patients due to inadequate blood pressure regulation and cerebral autoregulation, warranting further research.

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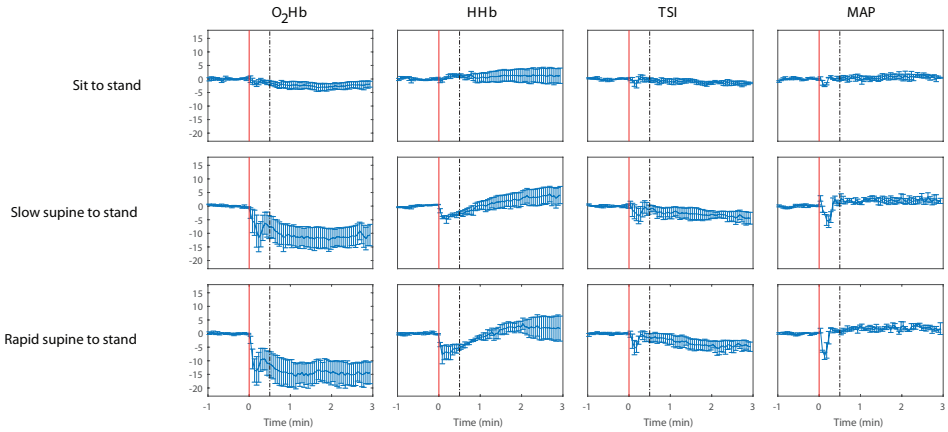
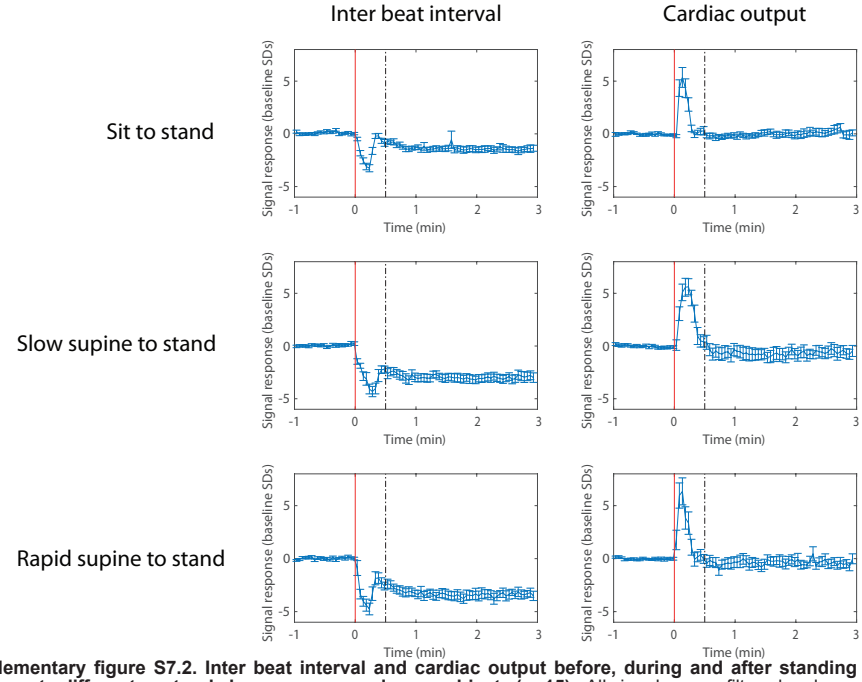
Supplementary material



Supplementary figure S7.1. O_2Hb, HHb, TSI and mean arterial pressure of the included female individuals before, during and after standing up as a response to different postural changes, averaged over subjects (n=3). All signals are unfiltered and normalized at baseline. The red vertical line indicates the onset of the postural change. The dashed line indicates the transition from the early (0 – 30 seconds) to the late (30 – 180 seconds) interval. The error bars indicate the standardized error of the mean.



Supplementary figure S7.2. Inter beat interval and cardiac output before, during and after standing up as a response to different postural changes, averaged over subjects (n=15). All signals are unfiltered and normalized at baseline. The red vertical line indicates the onset of the postural change. The dashed line indicates the transition from the early (0 – 30 seconds) to the late (30 – 180 seconds) interval. The error bars indicate the standardized error of the mean.

Chapter 8

Multimodal monitoring of cardiovascular responses to postural changes

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Abstract

Background: In the poorly understood relationship between orthostatic hypotension and falls, next to blood pressure (BP), baroreflex sensitivity (BRS) and cerebral autoregulation (CAR) may be key measures. The posture- and movement dependency of orthostatic hypotension requires continuous and unobtrusive monitoring. This may be possible using simultaneous photoplethysmography (PPG), electrocardiography (ECG) and near-infrared spectroscopy (NIRS) signal recordings, from which pulse wave velocity (PWV; potentially useful for BP estimation), BRS and CAR can be derived. The PPG, NIRS and PWV signal correlation with BP and BRS/CAR reliability and validity need to be addressed.

Methods: In 34 healthy adults (mean age 25 years, inter quartile range 22-45; 10 female), wrist and finger PPG, ECG, bifrontal NIRS (oxygenated and deoxygenated hemoglobin) and continuous BP were recorded during sit to stand and supine to stand movements. Sixteen participants performed slow and rapid supine to stand movements; eighteen other participants performed a 1-minute squat movement. Pulse wave velocity (PWV) was defined as the inverse of the ECG R-peak to PPG pulse delay; PPG, NIRS and PWV signal correlation with BP as their Pearson correlations with mean arterial pressure (MAP) within 30 seconds after the postural changes; BRS as inter beat interval drop divided by systolic BP (SBP) drop during the postural changes; CAR as oxygenated hemoglobin drop divided by MAP drop. BRS and CAR were separately computed using measured and estimated (linear regression) BP. BRS/CAR reliability was defined by the intra class correlation between repeats of the same postural change; validity as the Pearson correlation between BRS/CAR values based on measured and estimated BP.

Results: the highest correlation with MAP was found for finger PPG and oxygenated hemoglobin, ranging from 0.75-0.79 (sit to stand), 0.66-0.88 (supine to stand) and 0.82-0.94 (1-minute squat). BRS and CAR reliability was highest during the different supine to stand movements, ranging from 0.17 – 0.49 (BRS) and 0.42-0.75 (CAR); validity was highest during rapid supine to stand movements, 0.54 and 0.79 respectively.

Conclusion: PPG-ECG-NIRS recordings showed high correlation with BP and enabled computation of reliable and valid BRS and CAR estimates, suggesting their potential for continuous unobtrusive monitoring of orthostatic hypotension key measures.

Introduction

Orthostatic hypotension (OH), defined as a blood pressure (BP) drop of at least 20 mm Hg systolic and/or > 10 mm Hg diastolic after postural change,[1] is highly prevalent in older adults,[2–4] whereas the effectiveness of non-pharmacological interventions are limited.[5] OH may be accompanied by clinical symptoms, e.g. lightheadedness and dizziness,[6,7] and is associated with poor clinical outcome such as impaired physical performance,[8–10] falls,[11,12] cognition,[13] cardiovascular diseases[14,15] and mortality.[14–18] Sensitivity for the diagnosis of OH is higher for continuous BP measurement than for intermittent BP measurements after standing up, and continuous BP measurement has shown to be stronger associated with physical performance.[8,9] However, clinical orthostatic BP measurements do not account for many of the symptoms and falls patients experience at home, due to the time varying and posture- and movement dependent nature of orthostatic BP drop, resulting in a poor reproducibility of the OH diagnosis.[19] Furthermore, the baroreflex (i.e. change in interval between heart beats as a response to BP changes) and cerebral autoregulation (CAR, i.e. regulation of cerebral blood flow during BP changes) are mechanisms that potentially attenuate the clinical consequences of OH and are therefore essential to understand the relationship between OH and clinical outcome.[20–24] BRS and CAR are not addressed during regular clinical BP measurements.[25,26] There is therefore a need for continuous, unobtrusive, simultaneous assessment of orthostatic BP, baroreflex sensitivity (BRS) and CAR, which cannot be performed using the devices currently used in clinical practice.

Elucidation of the relationship between OH and clinical outcome (i.e. physical performance, cognitive performance and falls) through continuous assessment of BP, BRS and CAR in the home situation may be possible using a combination of non-invasive measurements, encompassing photoplethysmography (PPG), ECG and near-infrared spectroscopy (NIRS). PPG may enable monitoring BP in superficial arteries, e.g. the radial artery (wrist) or digital artery (finger). PPG amplitude was reported to correlate with BP.[27–32] When combined with ECG, PPG can be used to compute pulse wave velocity (PWV), a parameter reflecting both BP, arterial stiffness and arterial vasoconstriction.[33] To assess CAR, cerebral oxygenation measured using NIRS may be used as a proxy for cerebral blood flow.[34–36]

Prerequisites for clinical application of the BP, BRS and CAR monitor during postural changes are a) correlation of PPG, NIRS and derived PWV with BP after postural change, to enable BP estimation, b) good reliability and validity of BRS/CAR estimates and c) evidence for the potential additional value of BRS estimates assessed during postural change compared to conventional validated BRS measures assessed in rest. In the present proof-of-concept study in a cohort of healthy adults we will address these prerequisites during different types and speeds of postural changes by calculating the correlations between PPG, NIRS and PWV signals,

and measured BP; intra class correlation between repeats of postural changes; correlations between BRS/CAR estimates based on estimated and measured BP; and correlations between BRS assessed during postural change and in rest.

Methods

Thirty-four participants were recruited by oral and written advertisement in a university teaching setting at the Radboud University in Nijmegen, The Netherlands. Sixteen participants were primarily recruited from university students (subgroup 1), while 18 participants were primarily recruited from university employees (subgroup 2). Participants were included if they were younger than 65 years, and had no history of cardiovascular, respiratory or neurological disorders resulting in impaired functioning. All data and analysis scripts are available via the following link: http://hdl.handle.net/11633/di.dcn.DSC_62002451_01_149

Ethical approval

The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Faculty of Science of the Radboud University in Nijmegen. All participants signed informed consent.

Participant characteristics

Information about age, height, weight, handedness, alcohol usage, smoking habits and medication use was obtained from all participants.

Instrumentation

Two PPG sensors were customized to measure synchronized output signals with a sampling frequency of 1000Hz and were applied to the left radial artery (wrist) and digital artery (distal digital finger). The left arm was placed in a sling to minimize differences in height between the PPG measurement location and the heart. A digital tilt meter was attached to the participants' trunk to measure the angle relative to the horizontal plane and to identify the start of postural change. Data recording was performed using a customized application developed in MATLAB R2017b (MathWorks, Natick, United States).

Two PortaLite NIRS sensors (Artinis Medical Systems B.V., Elst, The Netherlands; sampling frequency of 50 Hz) were applied bilaterally to the forehead, approximately 2 cm above the eyebrows. Differential pathway factors were estimated based on wavelength and age.[37] Oxygenated hemoglobin (O_2Hb) and deoxygenated hemoglobin (HHb) were computed using the modified Lambert-Beer law.[38] Data recording was performed using Oyxsoft v3 (Artinis Medical Systems B.V., Elst, The Netherlands).

A 5-lead ECG and continuous BP and was measured using a Finapres non-invasive hemodynamics monitor (Finapres NOVA, Finapres Medical Systems,

Amsterdam, The Netherlands), and applied to the left middle finger. This monitor includes a module measuring the height of the finger relative to the heart to enable reconstruction of BP at heart level from BP at finger level.

A common analogue reference signal was imported into all devices to enable off-line synchronization of the signals. The reference signal consisted of a train of 16 pulses for each minute, each pulse train coding the time from the start of the experiment in minutes. Off-line synchronization and storage, and further analysis of the signals was performed using MATLAB R2017b (MathWorks, Natick, United States).

Protocol

Participants were asked to void urine before start of the experiment. Room temperature was kept between 20-23 degrees Celsius. Participants were stimulated to relax, instructed not to talk and to limit movements not related to tasks.

To keep the total measurement duration per participant within two hours, each of the two recruited subgroups underwent a different experimental protocol (Figure 8.1). Subgroup 1 performed the following postural changes: A (sit to stand, i.e. standing up from sitting position at the preferred speed of the individuals), B (slow supine to stand, i.e. standing up from supine position in approximately 10 seconds) and C (rapid supine to stand, i.e. standing up from supine position in approximately

Table 8.1: Participant characteristics, stratified by subgroups.

Characteristic	N	All (n = 34)	Subgroup 1 (n = 16)	Subgroup 2 (n = 18)
Age, years, median [IQR]	34	25 [22-45]	22.5 [21-24]	37.5 [26.5-56.0]
Male, n (%)	34	24 (70.6)	12 (75.0)	12 (66.7)
Height, m, median [IQR]	34	1.80 [1.72-1.85]	1.80 [1.75-1.86]	1.80 [1.67-1.85]
Weight, kg, median [IQR]	34	70.5 [65.8-75.0]	70.5 [67.3 – 74.8]	69.0 [63.8-76.5]
Right-handed, n (%)	34	29 (85.3)	16 (100)	13 (72.2)
Current smoking, n (%)	34	2 (5.9)	1 (6.3)	1 (5.5)
Excessive alcohol use, n (%)*	34	0 (0)	0 (0)	0 (0)
Medication use, n (%)	34	8† (23.5)	3 (18.8)	5 (27.7)
Resting HR, bpm, median [IQR]	34	71 [66 – 78]	71 [66-77]	71 [66-79]
Resting SBP, mmHg, median [IQR]	34	130 [123 – 140]	126 [122-140]	131 [126-145]
Resting DBP, mmHg, median [IQR]	34	82 [76-87]	79 [73-85]	83 [78 – 96]
Time needed for sit to stand, s, median [IQR]	34	7.0 [5.2-8.0]	6.6 [5.3-9.3]	7.0 [5.2-8.0]
Time needed for slow supine to stand, s, median [IQR]	16	15.6 [14.1-19.1]	15.6 [14.1-19.1]	NA
Time needed for rapid supine to stand, s, median [IQR]	16	6.7 [5.7-8.7]	6.7 [5.7-8.7]	NA
Time needed for supine to stand at preferred speed, s, median [IQR]	18	9.0 [6.8-11.4]	NA	9.0 [6.8-11.4]
Time needed for head up tilt, s, median [IQR]	18	16.4 [16.1-17.4]	NA	16.4 [16.1-17.4]

Resting HR, SBP and DBP were computed as the baseline mean. IQR: interquartile range; SD: standard deviation; BMI: Body Mass Index; HR: Heart rate; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure. *Excessive alcohol use is defined as > 14 units per week for females and > 21 units per week for males. † methylphenidate for attention deficit hyperactivity disorder (2 participants), terbutaline for asthma (2 participants), candesartan or hydrochlorothiazide for hypertension (2 participants), escitalopram for a mood disorder (1 participant), desloratadine for pollen allergy (1 participant).

3 seconds). Subgroup 2 performed postural changes A, D (supine to stand at preferred speed), E (head up tilt, i.e. tilting from supine position to 70-degree tilt in 15 seconds without use of leg muscles) and F (1-minute squat, i.e. an isometric leg exercise test increasing BP). Postural changes A-E were preceded by a 5-minute resting period (to reach steady state of BP regulation)[19] and followed by a 3-minute standing period.

All postural changes were performed in blocks of three repeats per block. Only two repeats per block were performed for postural change A and F in subgroup 2. The sequence of the blocks was randomized to prevent structural influences from preceding postural changes on following postural changes, except for the 1-minute squat blocks, which were performed at the end of the protocol as these postural changes might induce fatigue.

Signal quality assessment

PPG, NIRS and BP signals were inspected visually for each repeat of each postural change. Signals not showing a heartbeat for more than 10 seconds during baseline (i.e. the 60 seconds before testing), more than 10 seconds in the first minute after the start of the test or more than 20 seconds in minute two and three after the start of the test, were discarded.

Data preprocessing

PPG signals were filtered using a 0.05-10Hz Butterworth band pass filter to compute pulse wave velocity (PWV).[27,39,40] The PPG, NIRS and BP signals were resampled at 25 Hz. From these resampled signals, a standardized version (i.e. subtraction of baseline mean and division by baseline standard deviation) and a filtered version (using a 5-second moving average filter) were computed.

Pulse wave velocity (PWV) computation

Beat-to-beat PWV was computed using the ECG and the PPG signals and defined as the inverse of the time between the R-peak in the ECG to the peak in the first derivative of the PPG signal. Detection of peaks in the first derivative in the PPG signal was performed in two steps, to avoid detecting peaks not corresponding to the upstroke of the PPG wave on the one hand (i.e. a low specificity) and detecting no peaks at all (i.e. a low sensitivity) on the other hand. In the first step, a high specificity, low sensitivity PWV signal was computed, using high peak detection thresholds (i.e. 3 standard deviations of the surrounding 5 seconds of PPG signal). In the second step, a high sensitivity, low specificity PWV signal was computed using low peak detection thresholds (i.e. 1.5 standard deviations of the surrounding 5 seconds of PPG signal). To compute PWV for as many heartbeats as possible while preventing erroneous PWV calculation, the PWV values in the high sensitivity, low specificity signal exceeding the mean - 3 SD or + 5 SD of the high specificity, low sensitivity

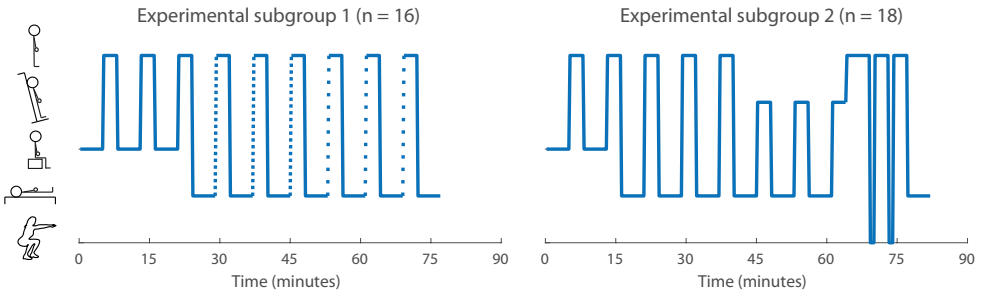

Figure 8.1. The experimental protocol for both subgroups (adapted from Mol et al., 2019). The symbols on the y-axis indicate (from top to bottom): active standing, head-up tilt, sitting, supine and squat position. Transitions shown as solid lines indicate preferred speed and dashed lines with small and wide gaps indicate rapid and slow transitions, respectively.

signals were discarded and the remaining signal was used for further analysis.

Signal correlation with BP

PPG, NIRS and PWV signal correlation with BP was defined as their correlation with mean arterial pressure (MAP) within 30 seconds after each postural change. Filtered signals (5 second moving average window) were used as these were reported to show the most clinically relevant representation of the BP data.[41] The signals were averaged over repeats.

Baroreflex sensitivity (BRS) and cerebral autoregulation (CAR)

BRS was defined as inter beat interval (IBI) drop divided by systolic BP (SBP) drop within one minute after postural change. CAR was defined as O_2Hb drop divided by MAP drop within one minute after postural change. All computations were performed using the 5-second moving average filtered signals. BRS and CAR values exceeding five times the standard deviation of the other measurements of the same postural change were discarded.

BRS and CAR were separately computed using measured BP and estimated BP (Figure 8.2). BP (both SBP and MAP) estimation was based on the finger PPG and performed for each participant, postural change (except the 1-minute squat) and repeat, by using linear regression models with the PPG and BP signals in the interval between 0-30 seconds as independent and dependent variables, respectively. For a given repeat, PPG and BP signals of the other available repeats of the same subject and postural change were used to compute the regression coefficients. BP was then estimated as: $BP = B_0 + B_1 * PPG$.

The following conventional validated BRS measures were assessed in rest: sequence method BRS and baroreflex effectiveness index (BEI).[42–45] Sequence method BRS and BEI were computed based on the 5-minute resting epochs preceding the sit to stand movements, using the criteria reported by Silva et al.[43]

Statistical analysis

Normally distributed continuous variables were presented using a mean and standard deviation. Variables following other distributions were presented using the median and inter quartile range.

Signal correlation with BP was expressed using Pearson correlation coefficients.

BRS and CAR reliability was defined as their two-way mixed absolute single measure intra class correlation (ICC) between repeats of the same postural change. ICCs between 0 – 0.40, 0.40 – 0.59, 0.60 – 0.74 and 0.75 – 1 were regarded as poor, fair, good and excellent, respectively.[46]

BRS and CAR validity was defined as the Pearson correlation between BRS/CAR estimates based on measured and estimated BP.

The potential additional value of BRS estimates assessed during postural

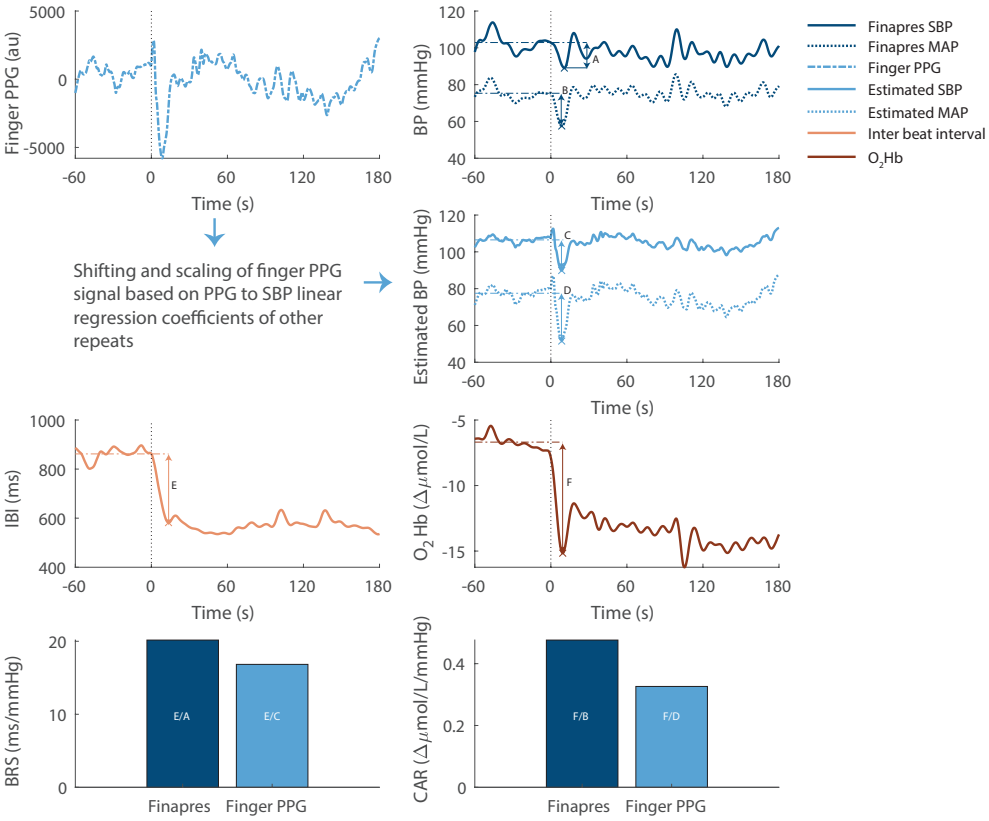

Figure 8.2. Example computation of baroreflex sensitivity and cerebral autoregulation for the first repeat of supine to stand at preferred speed in one participant. All signals are filtered using a 5-second moving average filter. The vertical dotted lines indicate the start of postural change, the horizontal dashed lines indicate baseline values and the crosses indicate the lowest value after standing up. As indicated in the bottom panels, baroreflex sensitivity is computed as inter beat interval drop (E) divided by the measured (A) or estimated (C) SBP drop. Similarly, cerebral autoregulation is computed as the cerebral oxygenation drop (F) divided by the measured (B) or estimated (D) MAP drop. PPG: photoplethysmography; au: arbitrary units; SBP: systolic blood pressure; IBI: inter beat interval; O2Hb: cerebral oxygenated hemoglobin. BRS: baroreflex sensitivity; CAR: cerebral autoregulation.

change compared to conventional validated BRS measures assessed in rest was expressed using their Pearson correlations, lower correlations indicating higher potential additional value.

RESULTS

Table 8.1 lists the participant characteristics. The median age of the 34 included individuals was 25 years (inter quartile range (IQR) 22-45; 10 female). Median age of subgroup 1 and 2 was 22.5 years (IQR 21-24) and 37.5 years (26.5-56), respectively, and the number of included female individuals was 4 and 6.

Signals

Signal quality assessment

After signal quality assessment, at least one repeat for each postural change was available for 31/34 subjects. The proportion of repeats showing good quality data was overall 329/355 (93%), and ranged among postural changes from 31/36 (86%; 1-minute squat) to 57/59 (97%; head up tilt). The proportion of signals discarded after visual quality inspection was 8.5% (wrist PPG), 4.9% (finger PPG), 1.3 % (NIRS) and 0.6% (BP). Table 8.2 and 8.3 show the available number of repeats per postural change and the number of repeats per signal discarded after data quality assessment, respectively.

Table 8.2: Data availability, repeats

	# Participants	# Repeats (# participants)	Repeats discarded*, # repeats (# participants)
Sit to stand	34	3 (16), 2 (18)	6 (5)
Slow supine to stand	16	3	5 (4)
Supine to stand at preferred speed	18	3	4 (3)
Rapid supine to stand	16	3	4 (4)
Head up tilt	18	3	2 (1)
1-minute squat	18	2	5 (3)

Data availability. Number of participants, number of repeats per participant and availability of extra repeat performed by second observer. *Repeats discarded due to technical problems affecting all signals such as problems with data storage or loss of the reference signal needed for proper synchronization of the signals.

Table 8.3: Data availability, signals

	Wrist PPG	Finger PPG	NIRS	BP
Sit to stand	8 (5)	4 (3)	0	0
Slow supine to stand	10 (5)	5 (2)	0	1 (1)
Supine to stand at preferred speed	1 (1)	2 (2)	0	0
Rapid supine to stand	8 (6)	3 (2)	2 (1)	1 (1)
Head up tilt	0	0	0	0
1-minute squat	1 (1)	2 (2)	2 (2)	0

The table lists the number of discarded repeats per signal, stratified by test condition. The values in parentheses indicates the number of participants for whom one or more repeats per signals were discarded.

Signal characteristics

Figure 8.3 shows the averaged signals during the sit to stand movement and appendix A (https://rb.gy/oqxwxe) additionally shows the responses to the supine to stand and head up tilt movements. The signals showed a similar response to sit to stand and supine to stand, and consisted of a temporary drop (BP, PPG, O_2Hb and HHb) or increase (heart rate and PWV) within 30 seconds after standing up, reaching a steady state at 60 seconds after standing up. The responses to head up tilt within 30 seconds were smaller than the responses to sit to stand and supine to stand movements.

Figure 8.4 shows the averaged signals during and after a 1-minute squat movement. All signals, except HHb showed an increase during squat. After standing up from squat position, wrist and finger PPG, O_2Hb and HHb and BP showed a sudden drop, heart rate declined slowly and PWV signals increased to rise, reaching a peak at 20-30 seconds after standing up and declining thereafter. Signal characteristics (means, minima and maxima) after postural changes and during and after the 1-minute squat movement are listed in Appendices B and C (https://rb.gy/oqxwxe).

Signal correlation with BP

Figure 8.5 shows the PPG, NIRS and PWV signal correlation with BP after postural change. Finger PPG and oxygenated hemoglobin signals showed highest signal correlation with BP, ranging from 0.75-0.79 (sit to stand), 0.66-0.88 (supine to stand) and 0.82-0.94 (1-minute squat).

Baroreflex sensitivity and cerebral autoregulation

Reliability and validity

Figure 8.6 shows BRS and CAR reliability and validity. BRS and CAR showed the highest ICC between repeats during supine to stand movements, ranging from 0.17 – 0.49 (BRS) and 0.42-0.75 (CAR). Correlation between BRS/CAR estimates based on measured and estimated BP was highest during rapid supine to stand movements, 0.54 and 0.79 respectively.

Potential additional value of BRS estimates assessed during postural change

Figure 8.7 shows the comparison between BRS estimates assessed during postural change and conventional validated BRS measures assessed in rest. BRS assessed during sit to stand and head up tilt was correlated with sequence BRS (r = 0.59 and 0.61, respectively). Correlations between supine to stand movements and sequence BRS in rest were low (r = -0.07 - 0.34). All baroreflex measures showed a low correlation with baroreflex effectiveness index (r = -0.33 – 0.35).

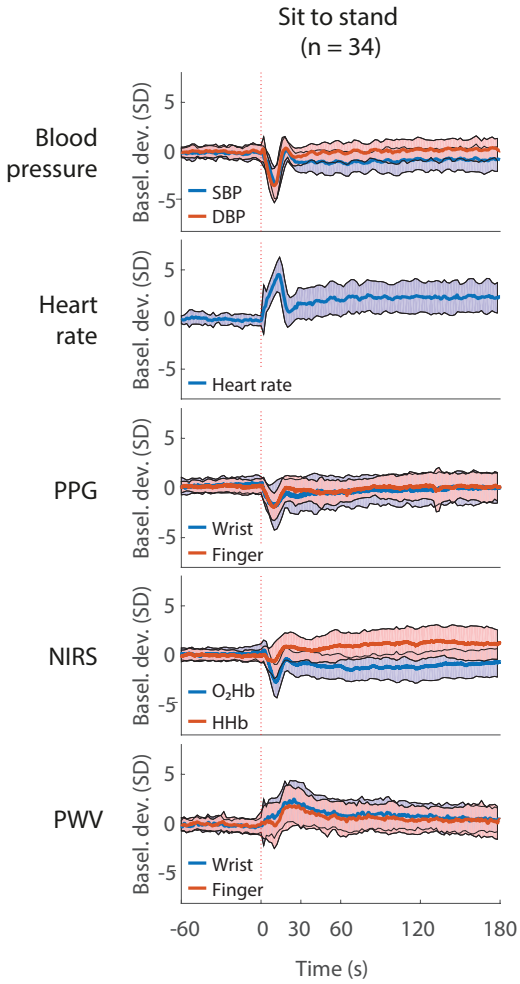

Figure 8.3. Average blood pressure, heart rate, photoplethysmography (PPG), near infrared spectroscopy (NIRS) and pulse wave velocity (PWV) during the sit to stand movement. All signals are unfiltered and normalized at baseline. The red vertical line indicates the onset of the postural change. The shaded areas indicate the standard deviation. The data represent 24 male subjects and 10 female subjects. Basel. dev.: signal deviation from mean baseline; SBP: systolic blood pressure; DBP: diastolic blood pressure; O_2Hb: oxygenated hemoglobin; HHb: deoxygenated hemoglobin.

Discussion

In this proof-of-concept study in a cohort of healthy adults we found that combined photoplethysmography (PPG), ECG and near-infrared spectroscopy (NIRS) signal recordings to estimate blood pressure (BP), baroreflex sensitivity (BRS) and cerebral autoregulation (CAR) during various postural changes showed high signal correlations with measured BP, particularly for finger PPG and NIRS derived oxygenated hemoglobin (correlations ranging from 0.66-0.94). Furthermore, we found that BRS

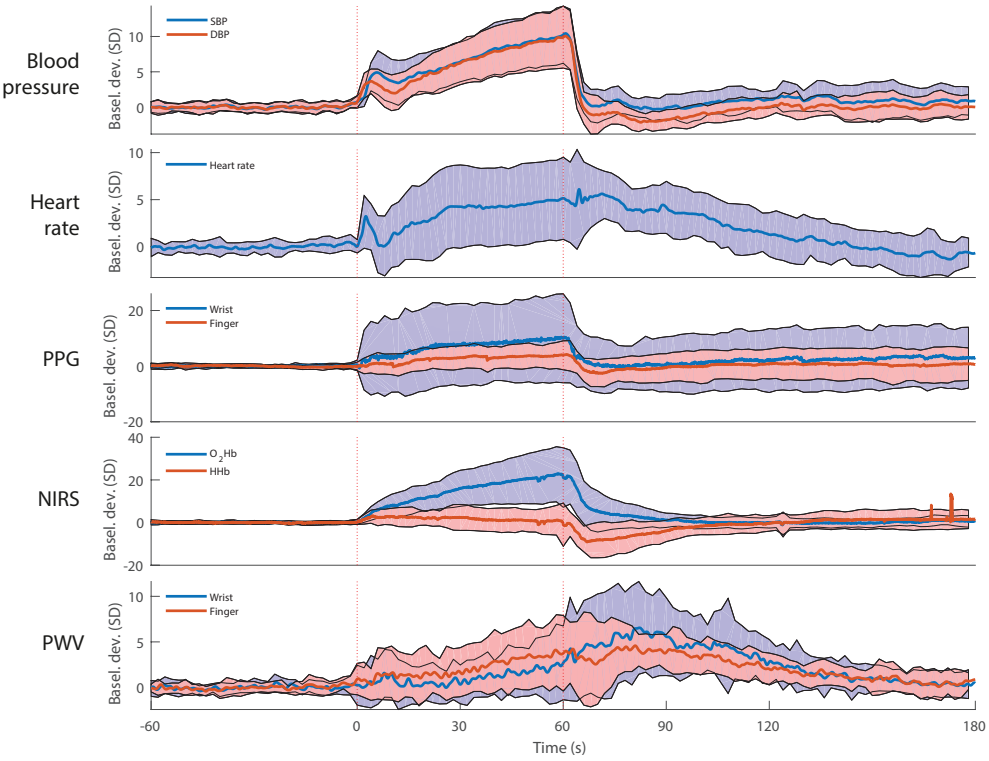

Figure 8.4. Average blood pressure, heart rate, photoplethysmography (PPG), near infrared spectroscopy (NIRS) and pulse wave velocity (PWV) during 1-minute squat movement. All signals are unfiltered and standardized at baseline. The red dotted vertical lines indicate the onset and end of the 1-minute squat movement. The shaded areas indicate the standard deviation. The data represent 12 male subjects and 6 female subjects. N = 18. O_2Hb: oxygenated hemoglobin; HHb: deoxygenated hemoglobin.

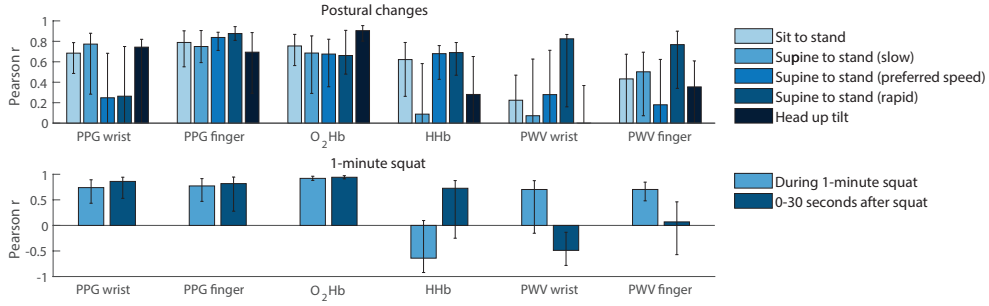

Figure 8.5. Signal correlation with blood pressure. Top panel: correlation with mean arterial pressure, evaluated over the first 30 seconds after postural change. All bars indicate the median and error bars indicate the inter quartile range. The data represent 24 male subjects and 10 female subjects. N = 34 (sit to stand), n = 16 (slow and rapid supine to stand) and n = 18 (supine to stand at preferred pace and head up tilt). Bottom panel: correlation with mean arterial pressure during and after the 1-minute squat movement. The data represent 12 male subjects and 6 female subjects (N = 18). HHb: deoxygenated hemoglobin; MAP: mean arterial pressure; O_2Hb: oxygenated hemoglobin; SBP: systolic blood pressure; SD: standard deviation; PPG: photoplethysmography; PWV: pulse wave velocity.

was of poor to fair reliability and CAR was of fair to excellent reliability during the supine to stand movements. Correlations between BRS/CAR estimates based on estimated and measured BP were 0.54 and 0.79, respectively. Correlations between BRS estimates assessed during postural change and conventional validated BRS measures assessed in rest were particularly low for supine to stand movements, indicating the potential additional value of the BRS estimates assessed during these postural changes. These results suggest the potential clincial value of these techniques for continuous and unobtrusive monitoring of blood pressure, BRS and CAR as key measures of orthostatic hypotension.

To the best of our knowledge, this is the first study proposing and assessing a non-invasive technique that might be used for continuous monitoring of posture-related BP, BRS and CAR in patients with OH. Results on sensitivity and reliability of NIRS parameters in a subpopulation of this study (n = 15) were published before.[36] Other previous research focussed on specific aspects, such as PPG-based BP estimation,[27,47] cerebral oxygenation changes during standing up[24,48,49] and posture related PWV changes,[50] but never assessed a combined ambulatory technique for BRS and CAR monitoring.

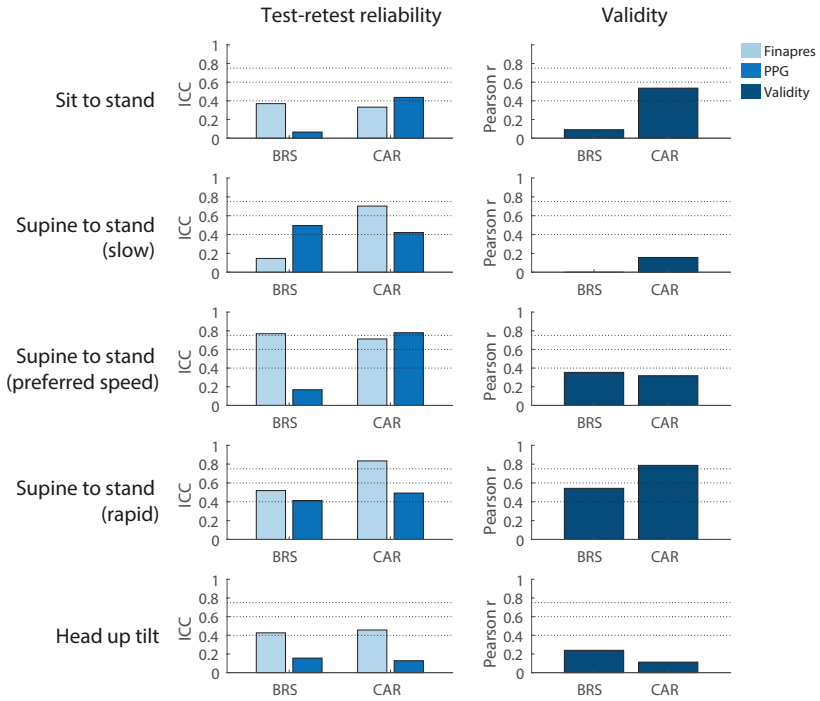

Figure 8.6. Baroreflex sensitivity and cerebral autoregulation. Reliability and validity for different postural changes. Reliability is shown for baroreflex sensitivity and cerebral autoregulation as assessed using the measured and estimated blood pressure. Rapid supine to stand gives most valid measurements of baroreflex and cerebral autoregulation. The data represent 24 male subjects and 10 female subjects. N = 34 (sit to stand), n = 16 (slow and rapid supine to stand) and n = 18 (supine to stand at preferred pace and head up tilt). BRS: baroreflex sensitivity; CAR: cerebral autoregulation; PPG: finger photoplethysmography.

Signal correlation with BP

The high correlation with BP found for finger PPG indicates that this signal might be used for continuous BP estimation during postural change. The high correlation of O_2Hb with BP was not expected, as O_2Hb is not only determined by BP, but also by CAR,[34,35] which may act as a high-pass filter,[51] and cerebral microcirculation.[52] The results of the present study indicate that BP is a relatively large contributor to cerebral oxygenation.

Finger PWV correlated well with BP during the rapid supine to stand movement, but not during other postural changess, potentially due to the fact that BP drop is largest during rapid supine to stand. However, PWV in theory also reflects arterial

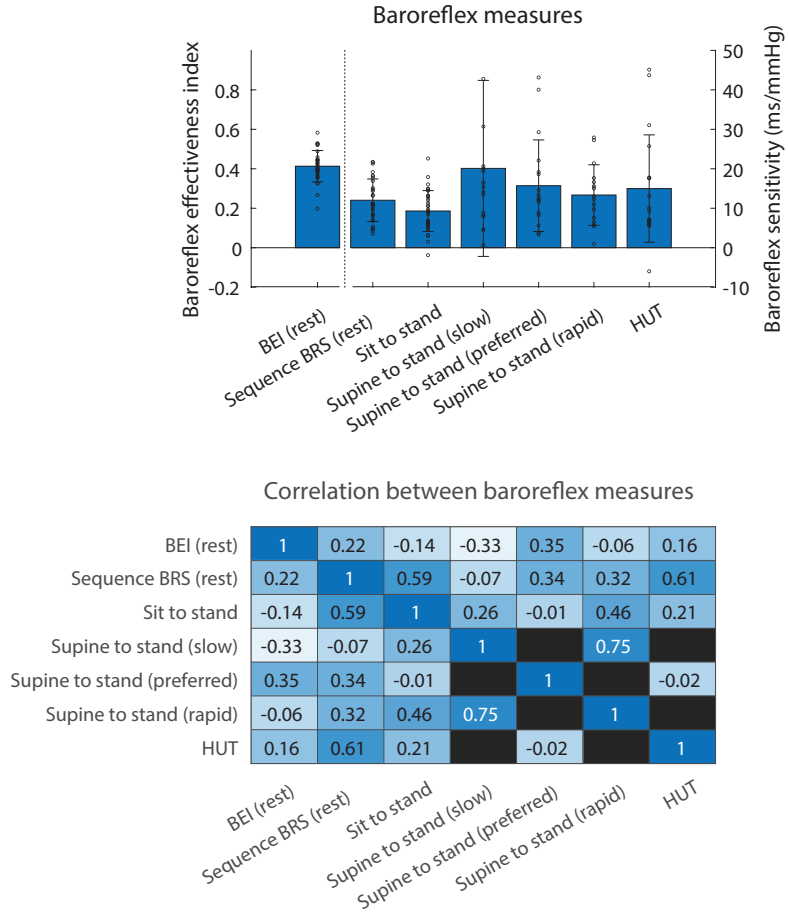

Figure 8.7. Comparison between baroreflex measures. Bars in the top panel show the mean of each baroreflex measure, error bars indicating the standard deviation and small circles the data points corresponding to individual subjects. The bottom panel shows the Pearson correlation coefficient of the correlation between the different measures. Empty squares indicate that the two baroreflex measures were not available for the same individuals. BEI: baroreflex effectiveness index; BRS: baroreflex sensitivity; HUT: head up tilt

stiffness and arterial vasoconstriction, which are of interest in patients with OH.[33] The association of PWV with arterial stiffness and arterial vasoconstriction was not addressed in the present study, but should be investigated in future studies by assessing the association of PWV with carotid intima-media thickness, as a measure of vessel stiffness,[53–55] and by measuring PWV during hand grip exercise, which influences vascular sympathetic outflow and thereby vasoconstriction.[56,57] If PWV can be demonstrated to be a good measure of vessel stiffness, it can potentially be used to differentiate between impaired baroreflex sensitivity from increased vessel stiffness and other (e.g. neural) causes.

Baroreflex sensitivity and cerebral autoregulation

BRS reliability was rather low, which may imply that more than three rapid supine to stand repetitions may be necessary to cancel out noise. CAR reliability and validity was higher compared to BRS reliability and validty, which may be explained by the many factors (e.g. emotions, mood, respiration) that influence inter beat interval,[58] which is used to compute BRS, but not CAR.

BRS and CAR showed highest validity when assessed during rapid supine to stand movement, potentially because PPG-ECG-NIRS signal to noise ratio is highest during this postural change.

BRS and CAR computation depends on a good BP estimation, for which an accurate model is necessary. In this study, simple linear regression models were used for to this end to provide first evidence that BP can be estimated from finger PPG signals. However, substantial inter- and intra-individual variation of the regression betas was observed, which implies frequent calibration is necessary to obtain accurate BP estimations. As this is impractical for the goal of continuous estimation of BP, BRS and CAR, more robust models should be developed to estimate BP from PPG-ECG-NIRS data, which may also incorporate heart rate and pulse wave velocity signals. This could be performed by training neural networks, warranting further research.

Correlations between BRS estimates assessed during postural change and conventional validated BRS measures assessed in rest were rather low, indicating the potential additional value of the BRS estimates assessed during these postural changes. The low correlation may be explained by the non-linear nature of the baroreflex, implying that a BP variation increase with a certain factor is not necessarily followed by a change in inter beat interval variation increase with the same factor.[59]

In the present study, BRS was defined as the inter beat interval drop divided by the SBP drop after standing up. The clinical value of this BRS measure needs to be further established by addressing its association with clinical phenotype, e.g. age, presence of orthostatic symptoms, and physical and cognitive performance. Furthermore, the underlying physiology should be elucidated by simultaneous measurements of muscle sympatetic nerve activity.[60] A proper functioning baroreflex

characterized by inter signal coupling of heart rate, blood pressure and muscle sympathetic nerve activity may be particularly related to clinical phenotype.[61] Development of barocontrol models is needed to further disentangle different components contributing to the baroreflex.[62]

As the NIRS-based measure of CAR used in the present study may apart from cerebral blood flow also be influenced by cerebral microcirculation, further external validation of this CAR measure using cerebral blood flow measurements should be performed in further research, as well as its association with clinical phenotype.

Accuracy of the BP measurements used as a gold standard

In this study, continuously and non-invasively measured peripheral BP was used to estimate central (aortic) BP, as in other studies.[63–68] Continuously and non-invasively measured peripheral BP was demonstrated to give a good approximation of intra-arterial radial BP in different clinical populations.[68–71]

BP drop after the head up tilt movement was smaller compared BP drop after the active stand movements. This is accordance with results reported in a previous study and may be due to a temporary muscle artery vasodilation during active standing up in contrast to passive tilt, decreasing BP.[72] This effect counteracts the BP increasing effect of muscle use during standing up through increased venous return and seems to outweigh it in the present and a previous study.[72]

Strength and limitations

The strength of this study is that it systematically assesses the PPG, NIRS and PWV correlation with BP after postural change and the reliability and validity of the derived BRS and CAR estimates.

The generalizibility of this study to the proposed target group of older adults with orthostatic hypotension is limited due to the young age of the investigated population. Though the investigated population was relatively healthy, some individuals in the investigated population used drugs affecting the cardiovascular system. Together with the relative underrepresentation of female participants (29.4 %), this limits the representativeness of the results for healthy adults. The difference in median age between the subgroups was rather large due to recruitment differences, which limits the comparability of the subgroups. This should be taken into account when comparing the results from two postural changes executed by the two different subgroups, e.g. the rapid supine to stand and supine to stand at preferred speed movements.

The absence of cerebral blood flow measurements as a gold standard for CAR measurements and the fact that 7% of the trials had to be discarded during some repeats due to technical problems or poor signal quality are limitions of this study.

Correlation of finger and wrist PPG with BP was computed while the arm was kept at heart height using a sling, which is a limitation for ambulatory applicability.

Future experiments should be independent of this design by correcting PPG based BP estimations for the difference in height between heart and PPG measurement site. This height difference therefore has to be measured separately.

The currently proposed model to estimate BP based on finger PPG is dependent on regular calibration of the data, which is an issue to be addressed in further research.

Clinical perspectives and future directions

Clinical application of the PPG-ECG-NIRS monitor requires several additional steps, i.e making the separate sensors entirely wireless, improving the BP estimation algorithms, making BP estimation independent of finger height relative to the heart and further validation of the BRS and CAR estimates in a clinical setting. When these requirements are met, PPG-ECG-NIRS could be applied in patients with impaired mobility or falls, as suspected due to inadequate BP regulation. The PPG-ECG-NIRS monitor should provide a personal risk profile of BP regulation during standing up, which may enable clinicians to personalize treatment, e.g. giving advice on lifestyle changes or revising medication.

Further research should address the association of the investigated parameters with healthy ageing and the occurrence of clinical orthostatic symptoms, mobility impairment and falls. It should further address the external validity of the CAR estimates using cerebral blood flow velocity measurements during postural changes. More robust models should be developed to be able to continuously monitor BP, BRS and CAR from PPG-ECG-NIRS signal recordings without the need for frequent calibration.

Conclusion

PPG and NIRS signals correlated with blood pressure in healthy adults, enabling blood pressure estimation. The BRS and CAR estimates derived from the PPG-ECG-NIRS signals were reliable and valid during supine to stand movements. This study provides evidence of the potential additional value of BRS estimates assessed during postural change compared to conventional validated BRS measures assessed in rest. The results suggest the potential clinical applicability of the PPG-ECG-NIRS signal recordings for continuous unobtrusive monitoring of blood pressure, BRS and CAR.

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Chapter 9

Pulse transit time as a proxy for vasoconstriction in younger and older adults

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Abstract

Objectives: Changes of vasoconstriction may be measured non-invasively using pulse transit time. This study assessed the sensitivity, test-retest reliability and validity of pulse transit time during vasoconstriction provocation and active standing, and the predictive value of pulse transit time for blood pressure drop.

Methods: Fifty-five younger (age < 65 years) and 31 older adults (age > 70 years) underwent electrocardiography, wrist and finger photoplethysmography and continuous blood pressure and total peripheral resistance measurements during vasoconstriction provocation using a cold pressor test (21 younger adults), or active stand tests (all other participants). Pulse transit time was defined as the time lag between the electrocardiography R-peak and the peak in the photoplethysmography first derivative; sensitivity as a significant decrease relative to baseline; test-retest reliability as the intra class correlation between different repeats of the same test; validity as the association between total peripheral resistance and pulse transit time; predictive value as the association between supine resting pulse transit time and mean arterial pressure drop during active standing.

Results: Finger pulse transit time was sensitive and reliable (ICC 0.2-0.8) during vasoconstriction provocation, but wrist pulse transit time was poorly reliable (ICC 0 – 0.5); only finger pulse transit time was sensitive to and reliable (ICC 0.4 – 0.8) during active standing in both younger and older adults. Finger pulse transit time was not associated with total peripheral resistance. Supine resting pulse transit time had predictive value for blood pressure drop during active standing in older adults (β -0.16; p 0.025).

Conclusions: Pulse transit time was sensitive to and reliable during vasoconstriction provocation and active standing, but did not significantly differ between younger and older adults. Pulse transit time could not be demonstrated to particularly reflect vasoconstriction, but it had predictive value for blood pressure drop during active standing.

Introduction

Arterial vasoconstriction may play a key role in orthostatic hypotension, a disorder of blood pressure regulation after active standing up, which is associated with negative health outcomes in older adults. [1–4] Arterial vasoconstriction leads to an increase in arterial stiffness, which is considered to be reflected by pulse transit time (PTT, i.e., the time it takes the blood pressure wave to travel along an arterial trajectory.[5–8] Decreased PTT was found to be associated with atherosclerosis and blood pressure dysregulation.[9–12] PTT can be measured non-invasively by a combination of electrocardiography and photoplethysmography ($PTT_{ECG\text{-}PPG}$), making it suitable for continuous and ambulatory monitoring during active maneuvers.[13,14]

These $PTT_{ECG-PPG}$ measurements however, may apart from vasoconstriction also be determined by blood pressure, inter beat interval, left ventricular ejection time and cardiac contractility.[15,16] To determine the potential use of $PTT_{ECG-PPG}$ as an ambulatory monitor of vasoconstriction and arterial stiffness, the following need to be assessed: $PTT_{ECG-PPG}$ sensitivity and test-retest reliability after vasoconstriction provocation and active standing; $PTT_{ECG-PPG}$ validity assessed as its association with total peripheral resistance (i.e., a reflection of vasoconstriction) compared to the other aforementioned physiological quantities; $PTT_{ECG-PPG}$ predictive value for blood pressure drop after standing up.

Previous studies showed significant PTT decreases in response to vasoconstriction provoking tests such as the cold pressor test (CPT)[17,18] and isometric hand grip test,[18–20] but these studies used PTT assessed at carotid and femoral artery or brachial artery and ankle, which is less suitable for ambulatory monitoring. Other studies reported a correlation between PTT and blood pressure during exercise tests, but did not address PTT during vasoconstriction provocation or active standing, and not in older adults.[13,21] One study assessed $PTT_{ECG-PPG}$ during CPT, but only during a short period of 30 seconds[22] and another study used $PTT_{ECG-PPG}$ during active standing and sustained handgrip for blood pressure estimation, but did not measure $PTT_{ECG-PPG}$ in older adults and only reported on the predictive value of $PTT_{ECG-PPG}$ for BP.[23]

This study aims to assess the sensitivity, test-retest reliability and validity of $PTT_{ECG-PPG}$ during CPT induced vasoconstriction provocation and active standing in both younger and older adults. This study also addresses the predictive value of $PTT_{ECG-PPG}$ for BP drop after standing up. It is hypothesized a) that $PTT_{ECG-PPG}$ decreases significantly during CPT and after active standing in younger and older adults; b) that $PTT_{ECG-PPG}$ after active standing shows a smaller decrease or larger increase in older adults compared to younger adults, as vasoconstriction is reported to become impaired with ageing;[24,25] c) that $PTT_{ECG-PPG}$ is valid, i.e., associated with total peripheral resistance rather than the other aforementioned physiological quantities; d) that supine resting $PTT_{ECG-PPG}$ has predictive value for blood pressure drop after active standing, as higher arterial stiffness is associated with impaired blood pressure restoration after standing up.[12]

Methods

Participants

Fifty-five adults aged below 65 years were recruited from students and employees of the Radboud University and 31 older adults aged above 70 years were recruited from Nijmegen sports centers and education centers for older adults. All participants signed informed consent and the study was approved by the ethical committee of the

Radboud University (ECS17022 and REC18021).

Age, height, weight and smoking habits were obtained using questionnaires. Arm span was measured as the distance between the tips of both middle fingers when the arms are spread.

Instrumentation

Two custom made photoplethysmography (PPG) sensors were applied to the wrist (radial artery) and distal phalanx of the index finger (digital artery). The sampling frequency was set at 1000 Hz.

To enable $PTT_{ECG-PPG}$ calculations, ECG was measured using a 5-lead ECG monitoring system (Finapres NOVA, Finapres Medical Systems, Amsterdam, The Netherlands; sampling frequency of 200 Hz).

Beat-to-beat blood pressure (i.e., mean arterial pressure (MAP) and pulse pressure (PP)) and inter beat interval (IBI) were monitored continuously (Finapres NOVA, Finapres Medical Systems, Amsterdam, The Netherlands) on the same arm. The modelflow algorithm employed by this device estimates total peripheral resistance (TPR), and left ventricular ejection time (LVET).[26] Cardiac contractility was estimated by the steepness of the blood pressure increase during systole (dPdt).

During the active stand test, the posture was measured using a tilt meter, which was attached to the participants' trunk.

Protocol

The room was kept at a temperature between 21 and 23 degrees Celsius. Participants were discouraged from talking during the experiment.

Figure 9.1 shows the protocol for all participants. Three trials of the cold pressor test were performed by a subgroup of younger adults (experimental subgroup 1, n = 21), consisting of a 5-minute resting period, followed by a 3-minute immersion of the hand in ice water and a 2-minute recovery through immersion of the same hand in a bath of water of 32 degrees Celsius. The hand that was used for the cold pressor

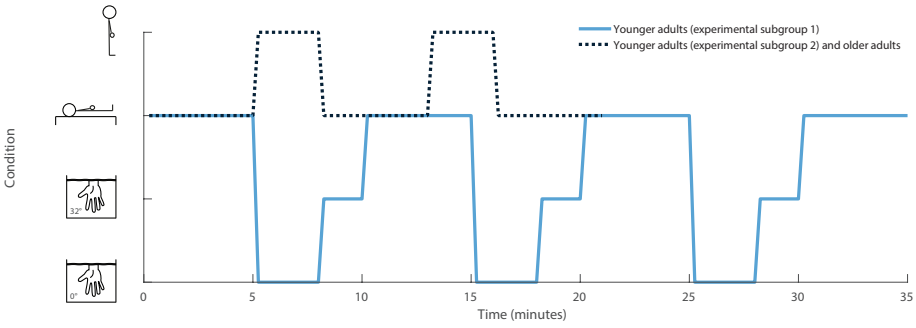

Figure 9.1. Protocol for both experimental subgroups of younger adults and for older adults. Symbols along the y-axis signify (from top to bottom): standing, supine rest, thermoneutral water immersion and the cold pressor test. °Degrees Celsius

test was randomized across participants. PPG and blood pressure measurements were acquired at the contralateral hand.

Two trials of the active stand test were performed by a subgroup of younger adults (experimental subgroup 2, n = 34) and by all older adults (n = 31). Participants were asked to stand up after a supine resting period of 5 minutes and keep standing for 3 minutes. During this test, the arm on which the PPG and BP measurements were performed was kept at heart height using a sling to eliminate hydrostatic pressure differences between heart and the left lower arm.

Data quality assessment and PTT computation

$PTT_{ECG-PPG}$ signals were computed from the wrist and finger PPG signals, hence referred to as wrist PTT and finger PTT.

PPG signals were filtered using a third order Butterworth bandpass filter with a passband from 0.1 to 5 Hz, after which the first derivative was computed. The first derivative was automatically assessed for signal quality based on the cross correlation of subsequent normalized 1-second data segments, assuming that a high-quality signal has high cross-correlation between subsequent segments due to the recurrent heartbeat. Segments with a cross-correlation lower than 0.5 with at least one adjacent segment were considered low quality and not used for PTT computation. A trial was discarded from further analysis if > 20% of the segments were of low quality.

An automatic peak detection algorithm was built to detect the R-peaks in the ECG and the peaks in the first derivative in the PPG signals using MATLAB R2017b (MathWorks, Natick, United States) and its signal analysis toolbox.

Table 9.1: Participant characteristics, stratified by subgroups

Characteristic	N	Younger adults, experi-mental subgroup 1 (n = 21)	N	Younger adults, experi-mental subgroup 2 (n = 34)	N	Older adults (n = 31)
Age, years, median [IQR]	21	21 [20-21.5]	34	25 [22-45]	31	77 [72-81]
Female, n (%)	21	6 (28.5)	34	10 (29.4)	31	17 (54.9)
Height, m, median [IQR]	21	1.79 [1.74-1.84]	34	1.80 [1.72-1.85]	31	1.69 [1.64 – 1.77]
Weight, kg, median [IQR]	21	70 [64.5-76]	34	70.5 [65.8-75.0]	31	74.0 [65.0 – 83.0]
BMI, kg/m^2, median, [IQR]	21	21.6 [21.6 – 23.6]	34	21.9 [20.9 – 23.2]	31	24.7 [23.4 – 27.0]
Current smoking, n (%)	21	0 (0)	34	2 (5.9)	31	0 (0)
Resting HR, bpm, median [IQR]	19	68 [66 – 71]	34	60 [55 - 71]	30	67 [63-77]
Resting SBP, mmHg, median [IQR]	19	121 [115 – 135]	34	124 [114 – 132]	30	153 [145 – 172]
Resting DBP, mmHg, median [IQR]	19	96 [88 – 108]	34	71 [64 – 84]	30	83 [77 – 94]
Resting pulse pressure, mmHg, median [IQR]	19	26 [21 – 30]	34	50 [44 – 60]	30	71 [64 – 78]
Resting wrist PTT, ms, median [IQR]	20	200 [188 – 219]	31	213 [200 – 228]	24	198 [180 – 229]
Resting finger PTT, ms, median [IQR]	20	230 [218 – 245]	32	252 [236 – 276]	18	261[219 – 285]

Resting HR, SBP and DBP were computed as the baseline mean. IQR: interquartile range; SD: standard deviation; BMI: Body Mass Index; HR: Heart rate; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Wrist and finger PTT were computed as the time between the R-peak in the ECG and the peak in the first derivative of the PPG signal. Furthermore, the difference between wrist and finger PTT was computed (PTT difference).

The quality of the resulting PTT signal was automatically assessed by computing the signal standard deviation per PPG signal (wrist and finger) and trial. PTT samples were discarded if they differed more than 3 standard deviations from the participant's mean.

Signal analysis

Baseline PTT, total peripheral resistance, blood pressure, inter beat interval, left ventricular ejection time and cardiac contractility were computed as the mean of the signal in the 60 seconds before start of the test condition. Means of twelve subsequent intervals of 15 seconds after the test start were computed for both the cold pressor test and the active stand test.

Statistical analysis

Continuous variables were reported as mean and standard deviation if normally distributed and as median and interquartile range in case of a non-normal distribution. Differences of the PTT signals with their baseline (i.e., sensitivity) were computed using the Wilcoxon signed rank test and differences between experimental subgroups were tested using the Mann-Whitney U test. Two-way mixed absolute single measure intra class correlations (ICC) were computed to express test-retest reliability. To assess validity, separate linear mixed models were developed with PTT as dependent variable and normalized (i.e., z-scored) TPR, MAP, PP, IBI, LVET and dPdt as fixed effect independent variables, allowing for random intercepts and random slopes among participants. PTT predictive value for MAP drop after standing up was assessed using linear mixed models with MAP drop as dependent variable and baseline PTT as fixed effect independent variable, allowing for random intercepts among participants.

Data availability

All data and analysis scripts are available via the following link: http://hdl.handle.net/11633/aacthxia.

Results

Table 9.1 lists the participant characteristics. The median age was 21, 25 and 77 years and the percentage of female participants was 28.5, 29.4 and 54.9 in younger adult experimental subgroups 1 and 2 and the group of older adults, respectively. The BMI in the respective groups was 21.6, 21.9 and 24.7 kg/m^2 and the only two participants currently smoking were in experimental subgroup 2 of younger adults. Wrist PTT was available for 20/21 younger (experimental subgroup 1), 31/34 younger (experimental

subgroup 2) and 24/31 older adults after data quality assessment. Finger PTT was available for 20/21 younger (experimental subgroup 1) 32/34 younger (experimental subgroup 2) and 18/31 older adults.

Sensitivity and reliability during the cold pressor test

Figure 9.2 shows the results of the cold pressor test in younger subjects. Both wrist PTT and finger PTT decreased significantly relative to baseline, but finger PTT decrease was larger and longer. The difference between wrist and finger PTT also decreased significantly relative to baseline. Test-retest ICCs were lower than 0.5 for wrist PTT. For finger PTT, ICCs were lower than 0.5 in intervals between 15 and 60 seconds after start of the cold pressor test. The difference between wrist and finger PTT had a low test-retest reliability (ICC < 0.5). TPR showed an inverse pattern to PTT, as well as MAP, PP and cardiac contractility. IBI and LVET showed a similar pattern as PTT.

Sensitivity and reliability during the active stand test

Figure 9.3 shows the results of the active stand test in younger and older adults. Wrist PTT significantly increased in young adults and only showed an initial significant decrease in older adults. Finger PTT significantly decreased in both younger and older adults. PTT difference significantly decreased only in young adults. Patterns of wrist PTT, finger PTT and their difference did not significantly differ between the young and older participants. TPR, MAP, PP and contractility showed an initial decrease followed by recovery, while a persistent decrease was shown by IBI and LVET. Test retest reliability ranged between 0.4 – 0.7 (wrist PTT, young adults), -0.2 – 0.6 (wrist PTT, older adults), 0.4 – 0.7 (finger PTT, young adults), 0.4 – 0.8 (finger PTT, older adults), -0.2 – 0.5 (PTT difference, young adults) and 0.1 – 0.5 (PTT difference, older adults).

PTT validity

Figure 9.4 shows the regression betas from the models explaining PTT from the physiological quantities (TPR, MAP, PP, IBI, LVET, contractility) both during the cold pressor test and the active stand test. None of the physiological quantities was found to significantly associate with changes in wrist PTT and PTT difference during the cold pressor test. MAP, PP and contractility were significantly negatively associated with finger PTT. TPR was not associated with finger PTT during the cold pressor test.

During the active stand test TPR was positively associated with wrist PTT, only in older adults. IBI and contractility were significantly associated with finger PTT and PTT difference only in young adults. PP was associated with PTT difference in young adults. TPR was not associated with finger PTT and PTT difference in either young or older adults.

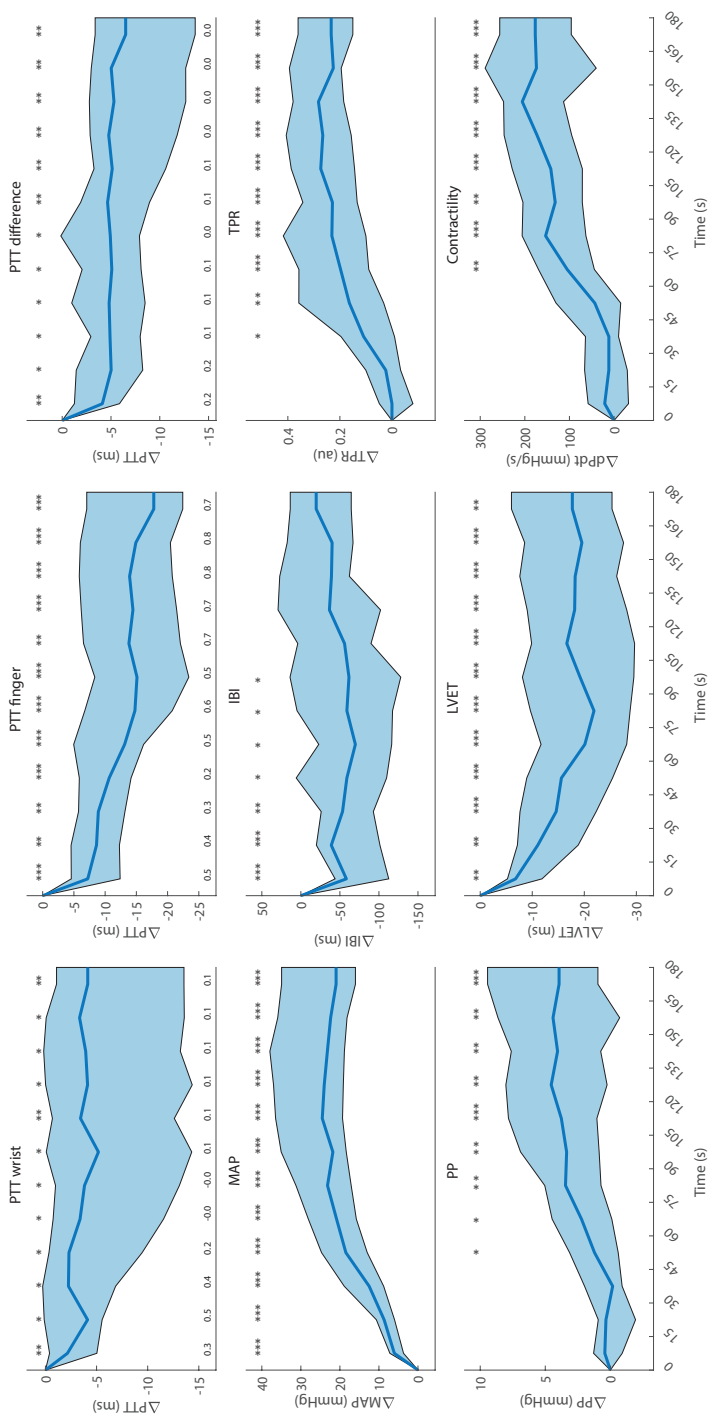

Figure 9.2. Pulse transit time (PTT), total peripheral resistance (TPR), mean arterial pressure (MAP), pulse pressure (PP), inter beat interval (IBI), left ventricular ejection time (LVET) and cardiac contractility during the cold pressor test in younger adults. The graphs show the median difference with baseline for each interval of 15 seconds. The shaded areas indicate the inter quartile ranges and one-three stars indicate statistically significant differences with baseline ($p < 0.05$, $p < 0.01$ and $p<0.001$, respectively). Time = 0 indicates the start of the cold pressor test. Test-retest reliability is expressed as intra class correlation (ICC) and shown for each interval and shown for each time interval at the base of the top panels.

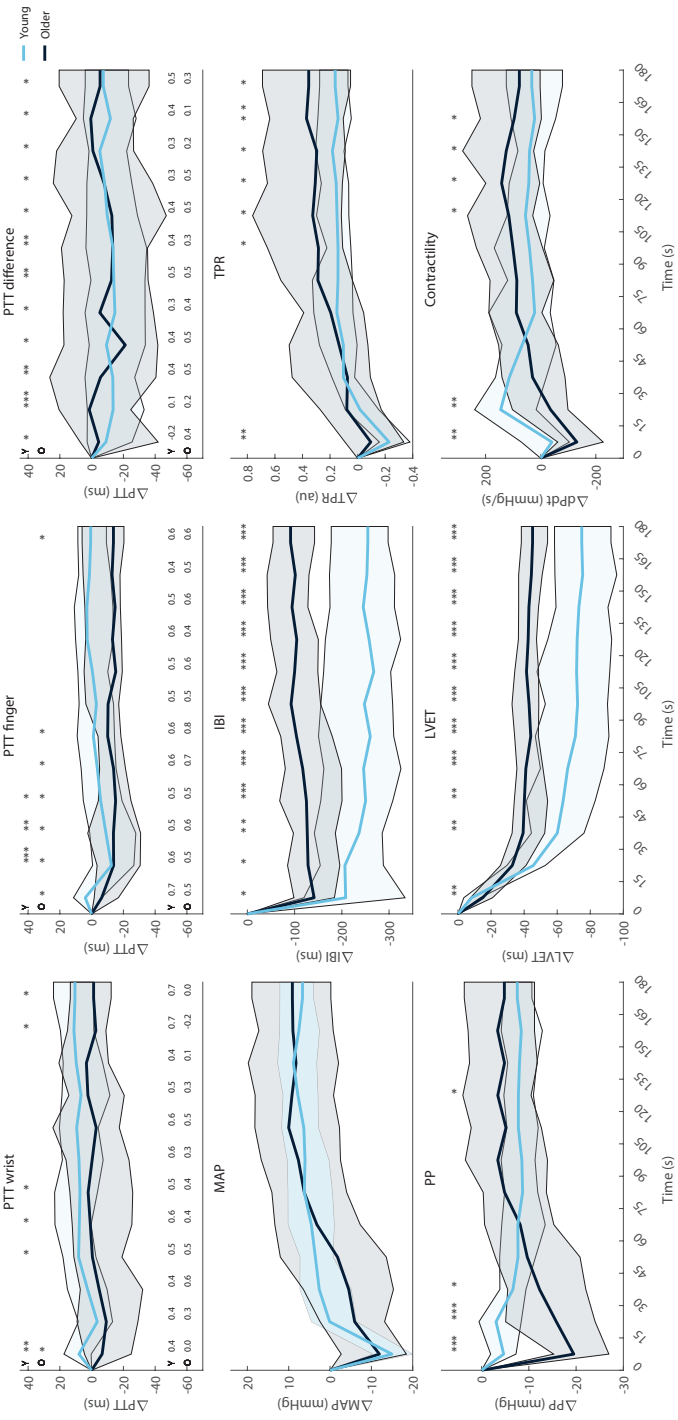

Figure 9.3. Pulse transit time (PTT), total peripheral resistance (TPR), mean arterial pressure (MAP), pulse pressure (PP), inter beat interval (IBI), left ventricular ejection time (LVET) and cardiac contractility during active standing in younger and older adults. The top panels show the course of median wrist PTT, finger PTT and the PTT difference after active standing as means of the consecutive 15-second intervals. Stars in the three top panels indicate statistical differences relative to baseline for the young (Y) and older (O) participants, 1-3 stars indicating p-values below 0.05, 0.01 and 0.001, respectively. There were no significant differences between younger and older adults. Test-retest reliability expressed as intra class correlations for each time interval are shown at the base of the top panels, both for the young and older participants. The lower six panels show the median course of TPR, MAP, PP, IBI, LVET and contractility. Stars in the lower six panels indicate statistically significant differences relative to baseline. Shaded areas in any panel indicate the inter quartile range.

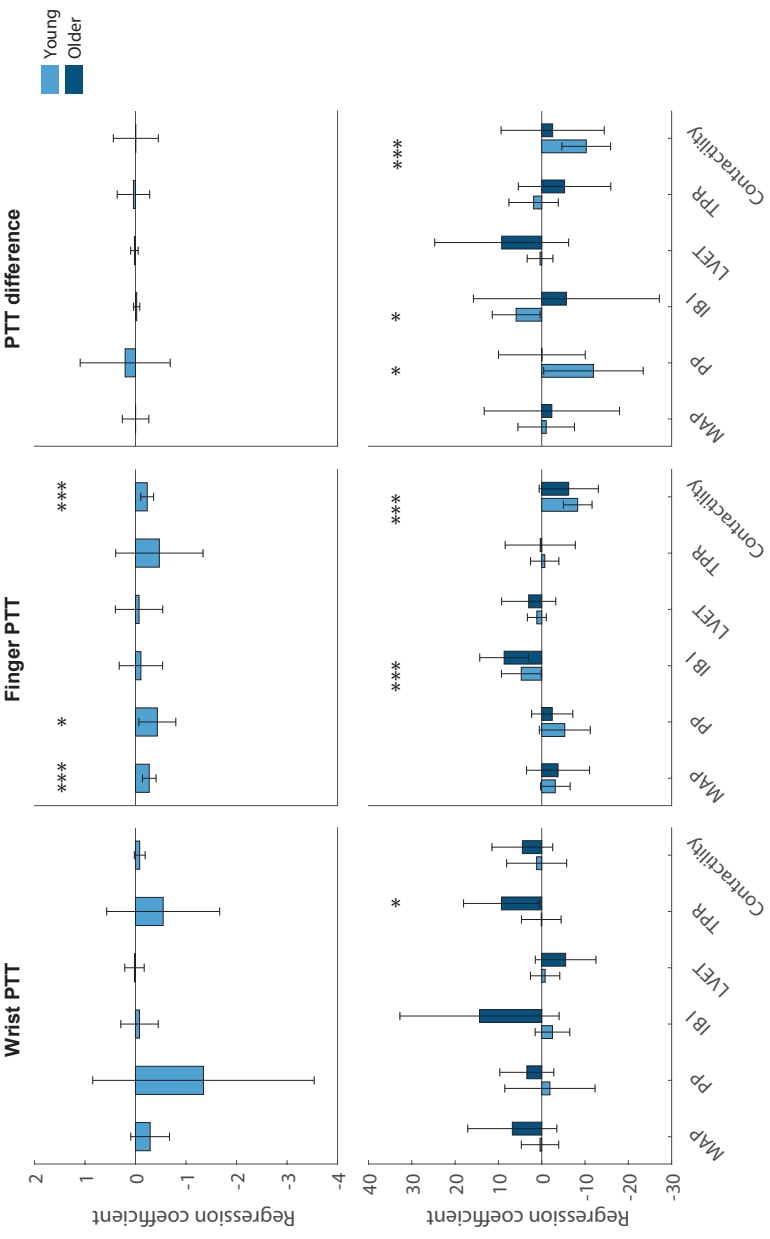

Figure 9.4. Associations between physiological quantities (TPR, MAP, PP, IBI, LVET and contractility) and PTT. The bars indicate the regression betas of the mixed linear models with PTT as dependent variable and the z-scored physiological quantity as dependent variable. The error bars indicate 95% confidence intervals. Stars indicate statistical significance baseline ($p < 0.05$, $p < 0.01$ and $p<0.001$, respectively). PTT: pulse transit time; CPT: cold pressor test; AST: active stand test; TPR: total peripheral resistance; MAP: mean arterial pressure; PP: pulse pressure; IBI: inter beat interval; LVET: left ventricular ejection time.

Supine resting PTT predictive value

Figure 9.5 shows the supine resting PTT of the younger and older adults who performed the active stand test and its predictive value for MAP drop after standing up. Neither wrist nor finger supine resting PTT nor PTT difference significantly differed between younger and older adults. Supine resting finger PTT was negatively associated with MAP drop after standing up (β = -0.16; 95% confidence interval = -0.30 – -0.02; p = 0.025).

Discussion

Wrist and finger pulse transit time determined using ECG and PPG ($PTT_{ECG\text{-}PPG}$) as well as their difference were sensitive (i.e., decreased significantly) during vasoconstriction provocation using a cold pressor test in young adults. Only finger PTT was sensitive to active standing in both young and older adults. PTT showed no statistically significant differences between age groups after active standing. Overall, test-retest reliability was highest for finger PTT, both during the cold pressor test active standing. PTT validity could not be demonstrated as neither wrist and finger PTT, nor PTT difference, was associated with total peripheral resistance as a reflection of vasoconstriction. Supine resting finger PTT had predictive value as it was negatively associated with mean arterial pressure (MAP) drop after standing up in older adults.

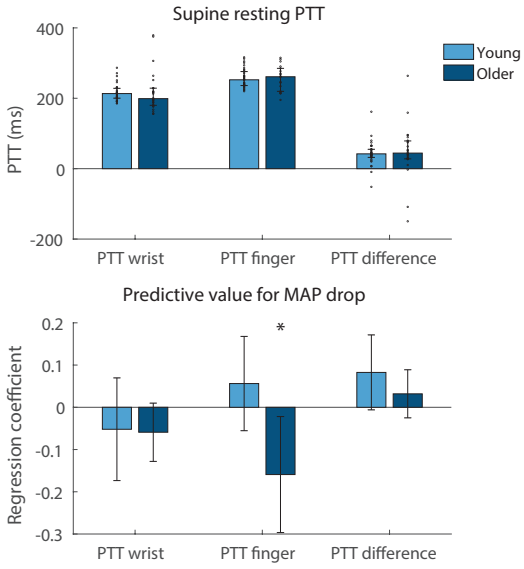

Figure 9.5. Supine resting pulse transit time (PTT) in younger and older adults and the predictive value for MAP drop after standing up. The upper panel shows supine resting PTT as the median (bar height), inter quartile range (error bars) and the mean values per participant (dots) for wrist PTT, finger PTT and PTT difference. There were no significant differences between younger and older subjects. The lower panel shows the regression coefficient of the predictive value of PTT for mean arterial pressure (MAP) drop after standing up. Error bars indicate 95% confidence intervals. The star indicates statistical significance.

Sensitivity

Wrist and finger PTT during the cold pressor test

The significant decrease of both wrist and finger PTT relative to baseline during CPT confirmed the hypothesis and suggests the potential value of PTT measured using ECG and wrist and finger photoplethysmography as a proxy for vasoconstriction.

Wrist and finger PTT during the active stand test

Wrist PTT did not significantly decrease in young adults and only showed a short initial decrease in older adults, which might be explained by a relatively large contribution of the pre-ejection period to wrist PPG. The significant decrease of finger PTT confirmed the hypothesis.

PTT difference during cold pressor test and active stand test

PTT difference decreased both during the cold pressor test and the active stand test only in young adults, suggesting that PTT difference may reflect vasoconstriction. The finding that PTT difference did not significantly decrease during the active stand test in older adults might indicate that vasoconstriction is impaired in older adults, but may also be caused by the large variance within the group of older participants. This variance should be further investigated in further studies as it may reflect the compensatory capacity of the peripheral arteries.

The PTT difference measure has the advantage of particularly reflecting the arterial trajectory between wrist and finger, which is mainly of the muscular artery type that is able to constrict and therefore a suitable trajectory to assess vasoconstriction.[27] Furthermore, unlike wrist and finger PTT, PTT difference eliminates the pre-ejection period, i.e. the time between electrical and mechanical activation of the heart, which may vary within and between individuals and is not a reflection of vasoconstriction.[28–30] However, no linear relationship between total peripheral resistance and PTT difference was found in the present study, either during the cold pressor test or during the active stand test.

Older compared to young adults

Wrist and finger PTT showed no significant differences between younger and older adults after active standing, contrary to the hypothesis. Absence of the expected differences may be due to the fact that the included population of older adults in this study used to exercise regularly, which slows down vascular ageing.[31] Future studies should investigate wrist and finger PTT during active standing in individuals with more progressed vascular ageing and atherosclerosis, to investigate whether wrist and finger PPG discriminate between these patients. As the variance within the groups was high, inter-individual differences should be addressed in further research as they may reflect the efficacy of cardiovascular adaptions after active standing and hence may determine clinical outcome.

Test-retest reliability

Overall, test-retest reliability was higher for finger PTT than for wrist PTT, potentially due to the smaller distance between the finger PPG sensor and the digital artery than between the wrist PPG sensor and the radial artery. The larger arterial trajectory assessed by finger PTT compared to wrist PTT renders finger PTT susceptible to more sources of noise and is hence unlikely to explain this result.

Validity

TPR was not significantly associated with either wrist or finger PTT or PTT difference during the cold pressor test. During the active stand test, TPR was not associated with finger PTT and PTT difference. These results might be explained by the absence of any relationship between total peripheral resistance and PTT, a the presence of a non-linear relationship which was not accounted for by the linear models, or limited reliability of the total peripheral resistance estimates derived from the modelflow algorithm implemented in the used Finapres device. Changes in pre-ejection period during the cold pressor test and the active stand test may have had a large contribution to wrist and finger PTT, potentially explaining the absence of an association with TPR. However, pre-ejection period has not contributed to PTT difference, which was not associated with TPR either. Future research should measure PTT, TPR and sympathetic efferent nerve activity and pre-ejection period simultaneously to further assess the validity of PTT and TPR as a measure of vasoconstriction and eliminate the effect of pre-ejection period.[25]

Predictive value of supine resting PTT

The observation that supine resting finger PTT was significantly associated with mean arterial pressure drop after standing up confirmed our hypothesis. The association was only present in older adults, suggesting that younger adults have not yet developed a vessel stiffness level that impairs the baroreflex as much as older adults.[32] However, this was not supported by a significantly lower supine resting PTT in older compared to younger adults. To further establish the value of supine resting wrist and finger PTT as a measure of arterial stiffness, its association with established techniques such as arterial ultrasound intima-media thickness measurements and aortic pulse wave velocity measurements should be addressed.

Signal quality

Low PPG signal quality prevented PTT calculation for approximately one tenth of the PPG signals in younger adults and approximately one third of the PPG signals in older adults, indicating that it is more challenging to obtain good quality PPG signals from older adults. This may be due to a thicker layer of subcutaneous fat between PPG sensor and the artery, which reduces the detected light intensity by PPG. Combining multiple small PPG sensors in one measurement unit would potentially

enable canceling out random noise by averaging over the sensors.

Strength and limitations

The strength of this study is that it systematically assessed the sensitivity, test-retest reliability and validity of $PTT_{ECG-PPG}$, which is potentially suitable for ambulatory use in the home situation, both during a strong standardized vasoconstriction provocation (i.e., the cold pressor test) and during active standing. Comparison with gold standard measurements for vasoconstriction and arterial stiffness are required to elucidate the vascular activity underlying the present results. Furthermore, the relatively large part of PPG signals in older adults that could not be used to compute PTT due to low signal quality is a limitation of the study.

Conclusion

$PTT_{PPG-ECG}$, particularly finger PTT, is sensitive to and reliable during vasoconstriction provocation and active standing. $PTT_{PPG-ECG}$ was not sensitive to discriminate between different age groups in the present study. $PTT_{PPG-ECG}$ could not be demonstrated to be valid, i.e., associated with total peripheral resistance. Supine resting finger PTT has predictive value for mean arterial pressure drop during active standing.

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Chapter 10

Orthostatic cerebral oxygenation and baroreflex sensitivity are associated with age and depend on the type of postural change

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Abstract

Purpose: Understanding the relationship between orthostatic hypotension and clinical outcome in older subjects may require assessing potential compensatory mechanisms. The purpose of this study was to assess measures of orthostatic cerebral oxygenation (as a proxy for cerebral autoregulation) and baroreflex sensitivity (BRS) with regard to their association with age and their dependence on the type of postural change (i.e., standing up from sitting versus standing position).
Methods: 34 younger (age < 65 years) and 31 older adults (age > 70 years) underwent continuous measurements of blood pressure (BP), electrocardiography (ECG), and oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin using near-infrared spectroscopy (NIRS) during standing up from sitting and supine position. BRS was defined as ECG-derived inter beat interval drop divided by systolic BP drop.
Results: Orthostatic O_2Hb and HHb drop were smaller in older compared to younger adults ($p < 0.01$), but recovery was slower ($\Delta = 2.8$ seconds, $p = 0.037$). BRS was lower in older adults ($\Delta = 5.3$-7.9 ms/mmHg, $p < 0.001$). O_2Hb drop amplitude was larger after standing up from supine position compared sitting position in both younger ($p < 0.001$) and older ($p = 0.036$) adults.
Conclusion: Assessment of compensatory mechanisms in orthostatic hypotension may be of additional value. The results suggest that orthostatic cerebral oxygenation drop is mitigated in older adults, albeit slower compared to younger adults and dependent on the type of postural change. The lower BRS in older adults suggests their higher vulnerability for orthostatic hypotension.

Introduction

Orthostatic hypotension (OH), defined as a sustained systolic/diastolic blood pressure (BP) drop of more than 20/10 mmHg within 3 minutes after standing up,[1] is associated with poor clinical outcome, such as cognitive impairment, cardiovascular disease, falls and mortality.[2–5] Impaired compensatory mechanisms such as cerebral autoregulation (aiming to attenuate cerebral blood flow and cerebral oxygenation fluctuations during orthostatic BP drops) and the baroreflex (aiming to restore BP by increasing heart rate increase and arterial vasoconstriction) may explain the relationship between OH and poor clinical outcome,[6,7] and are expected to associate with age and the type of postural change (i.e., standing up from sitting or supine position).[6,8,9]

Previous studies were inconclusive on the association between orthostatic cerebral oxygenation drop (as a proxy for cerebral autoregulation) measured with near-infrared spectroscopy (NIRS) and age. Smaller,[10] similar,[11] and larger[12,13] cerebral oxygenation drops in older adults compared to younger adults have

been reported. Furthermore, the effect of the type of postural change on cerebral oxygenation drop was not investigated. Previous studies on the association between baroreflex sensitivity (BRS, i.e., change in heart rate divided by change in BP) and age did not assess BRS during postural change, but in rest, during the Valsalva maneuver or during intravenous administration of vasopressor medication.[14–16]

This study assessed the association between measures of orthostatic cerebral oxygenation and BRS and age, and the influence of the type of postural change on these measures. It was hypothesized a) that the orthostatic cerebral oxygenation drop is larger and recovers slower in older adults compared to younger adults; b) that baroreflex sensitivity is lower in older adults compared to younger adults; c) that cerebral oxygenation drop is larger after standing up from supine position compared to standing up from sitting position in both younger and older adults. Test-retest reliability was assessed as an indication of the robustness of the measurements.

Methods

Participants

Thirty-four younger adults aged below 65 years and 31 older adults aged above 70 years were recruited using oral and written advertisements. Younger adults were recruited within the Radboud University, the Netherlands. Participants were included if they had no history of cardiovascular, respiratory or neurological disorders resulting in impaired functioning. The older adults were recruited from the Nijmegen sport centers, tennis and swimming clubs, education programs for older adults, and by advertisements in a local newspaper. Older adults were included if they were community-dwelling, able to walk at least 250 meters without the use of walking aids, independent for activities of daily living and not using antihypertensive medication. All participants signed informed consent and the study was performed in accordance with the Declaration of Helsinki and approved by the Ethics committee of the Faculty of Science of the Radboud University, Nijmegen.

Participant characteristics

Information about age, height, weight, handedness, alcohol usage, smoking habits, morbidity and medication use was obtained from all participants. Excessive alcohol use was defined as > 14 units per week for females and > 21 units per week for males.

Instrumentation

Beat-to-beat blood pressure and a 5-lead electrocardiogram (ECG) was continuously measured (Finapres NOVA, Finapres Medical Systems, Amsterdam, The Netherlands; sampling frequency of 200 Hz).

Cerebral oxygenation was measured bilaterally on the forehead using two

Portalite NIRS systems (Artinis Medical Systems B.V., Elst, The Netherlands; sampling frequency of 50 Hz). The differential pathway factor (DPF) for the NIRS measurements expresses the ratio of the real distance light has to travel through the tissue relative to the shortest distance. The DPF was used to compute oxygenated and deoxygenated hemoglobin (O_2Hb and HHb).[17] The DPF was computed according to the Scholkmann formula and set to 6.61 in the older group, as this value corresponds to the highest age (i.e., 50 years) for which the Scholkmann formula is validated.[17]

Posture was measured continuously by the tilt of the participant's trunk relative to the horizontal plane.

Protocol

Participants were asked to void urine before start of the experiment. A comfortable environment with a temperature of 20-22 degrees was pursued.

The protocol consisted of two types of postural changes, and two trials for each postural change: 1) sit to stand, i.e., sitting quietly for 5 minutes, standing up and stay in standing position for 3 minutes; 2) supine to stand, i.e., lying in supine position for 5 minutes, standing up and stay in standing position for 3 minutes. The sequence of the types of postural changes was randomized.

Data quality assessment

The duration of standing up was computed based on tilt meter data. Trials were discarded if standing up lasted longer than 10 seconds.

BP, ECG and NIRS signal quality was assessed based on the visibility of a heartbeat. Signals not showing a heartbeat for more than 10 seconds during baseline (i.e. the 60 seconds before testing), more than 10 seconds in the first minute after the start of the test or more than 20 seconds in minute two and three after the start of the test, were discarded.

Data analysis

Data analysis was performed using MATLAB R2019b (MathWorks, Natick, United States). The BP and cerebral oxygenation signals were resampled at a uniform sampling frequency of 10 Hz and filtered using a 5-second moving average filter. Left and right NIRS signals were averaged. In each signal, baseline was defined as the mean of the 60 seconds before standing up.

Blood pressure and cerebral oxygenation

Initial drop amplitude, initial recovery amplitude and time, and late recovery amplitude were determined for BP and cerebral oxygenation. Initial drop amplitude was defined as the lowest value within 30 seconds after standing up minus baseline; initial recovery amplitude as the value of the first peak after the initial drop minus baseline;

initial recovery time as the time from the start of standing up to the first peak after the initial drop. Initial recovery time was not computed for HHb as HHb typically does not show a peak after the initial drop. Late recovery amplitude was defined as the mean in the interval between 60 and 180 seconds after standing up minus baseline.

Baroreflex sensitivity (BRS)

BRS during supine rest was defined as the gain of the transfer function between BP and IBI in the frequency range between 0.05 and 0.15Hz.[18,19]

BRS during standing up was defined as the drop of the interval between subsequent R-peaks in the ECG (inter beat interval, IBI) divided by systolic BP drop.[20] The BRS values were averaged over trials and values exceeding 2.5 times the group standard deviation were discarded. Heart rate increase divided by systolic BP drop after standing up from supine position (dHR/dSBP) was computed to indicate whether OH might be neurogenic or non-neurogenic.[21]

Statistical analysis

All statistical analysis was performed using the statistics toolbox of MATLAB R2019b (MathWorks, Natick, United States). Normally distributed variables were reported using mean and standard deviation (SD); non-normally distributed variables using median and inter quartile range (IQR). Differences between younger and older adults were tested using the Mann-Whitney U test and differences between standing up from sitting and supine position using the Wilcoxon signed rank test. Significant BRS differences between age groups were further tested using linear regression

Table 10.1. Participant characteristics, stratified by age groups

Characteristic	Younger adults (n = 34)	Older adults (n = 31)
Age, years, median [IQR]	25 [22-45]	77 [72-81]
Female, n (%)	10 (29.4)	17 (54.9)
Height, m, median [IQR]	1.80 [1.72-1.85]	1.69 [1.64 – 1.77]
Weight, kg, median [IQR]	70.5 [65.8-75.0]	74.0 [65.0 – 83.0]
Current smoking, n (%)	2 (5.9)	0 (0.0)
Excessive alcohol use, n (%)[a]	0 (0.0)	1 (3.2)
Medication use, yes, n (%)	8 (23.5)	7 (22.5)
SPPB score, median [IQR]	NA	11 [11 – 12]
Handgrip strength males, kg, mean (SD)	NA	35.8 (6.3)
Handgrip strength females, kg, mean (SD)	NA	25.5 (5.4)
MOCA score, median [IQR]	NA	26 [25 – 28]
Resting HR, bpm, mean (SD)	64.8 (9.9)	68.8 (8.6)
Resting SBP, mmHg, median [IQR]	128 [122 – 130]	139 [126 – 155]
Resting DBP, mmHg, median [IQR]	79 [74 – 84]	82 [74 – 88]
Resting PP, mmHg, median [IQR]	49 [44 – 52]	56 [52 – 67]
Initial orthostatic hypotension, n (%)[b]	20 (58.8)	18 (58.1)
Orthostatic hypotension, n (%)[c]	1 (2.9)	1 (3.2)

Resting HR, SBP, DBP and PP were measured using a sphygmomanometer in sitting position. IQR: interquartile range; SD: standard deviation; BMI: Body Mass Index; SPPB: Short Physical Performance Battery; HR: Heart rate; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP pulse pressure; NA: not available. [a]Excessive alcohol use is defined as > 14 units per week for females and > 21 units per week for males. [b]Defined as a SBP drop > 40 mmHg and/or a DBP drop > 20 mmHg within 15 seconds after standing up. [c]Defined as a SBP drop > 20 mmHg and/or a DBP drop > 10 mmHg sustained until at least 60 seconds after standing up.

analysis, with and without correction for sex to test for the potential confounding role of sex.[14,22] The test-retest reliability of the aforementioned measures was expressed using two-way mixed intra class correlations (ICC). ICC scores between 0 – 0.40, 0.40 – 0.59, 0.60 – 0.74 and 0.75 – 1 were regarded as poor, fair, good and excellent, respectively.[23] Statistical significance was set at 0.05.

Results

Table 10.1 lists the participant characteristics. The median age of the participants was 25 years (IQR = 22 – 45) in the younger group and 77 years (IQR = 72 – 81) in the older group. 29.4% and 54.9% of the participants were female in the younger and older group, respectively.

After data quality assessment, BP and heart rate (HR) data during sit to stand was available in 31/34 younger adults and 30/31 older adults; during supine to stand in 28/34 younger adults and 29/31 older adults. Cerebral oxygenation data during sit to stand was available in 31/34 younger adults and 30/31 older adults; and during supine to stand in 28/34 younger adults and 28/31 older adults.

Signal characteristics

Figure 10.1 shows the mean BP, HR and NIRS cerebral oxygenation course during standing up in younger and older adults. During both types of postural changes, BP and cerebral oxygenation signals showed an initial drop and recovery (< 30 seconds) while HR showed an increase in this interval. The BP, HR and cerebral oxygenation signals reached steady state between 60 and 120 seconds.

Younger versus older adults

Cerebral oxygenation

Figure 10.2 shows the drop and recovery of BP and cerebral oxygenation after standing up from supine position. Initial O_2Hb and HHb drop amplitude was significantly smaller in older adults compared to younger adults (Δ = 4.6 µmol/L ($p < 0.001$) and 0.61 µmol/L ($p = 0.003$), respectively). Initial O_2Hb recovery amplitude was not significantly different between the age groups. Initial O_2Hb recovery time was significantly longer in older adults compared to younger adults (Δ = 2.8 seconds, $p = 0.037$). Late O_2Hb recovery amplitude was higher in older adults compared to younger adults (Δ = 5.0 µmol/L, $p = 0.004$), but late HHb recovery amplitude was not significantly different.

Baroreflex sensitivity

Figure 10.3 shows BRS in younger and older adults. BRS was significantly lower in older adults compared to young adults during supine rest (Δ = 6.11 ms/mmHg, $p < 0.001$) and standing up from sitting and supine position (Δ = 5.3 ms/mmHg ($p < 0.001$) and 7.9 ms/mmHg ($p < 0.001$), respectively). The linear regression coefficients

of the association between age group and BRS assessed during supine rest, sit to stand and supine to stand were -7.3 (95% confidence interval (CI) = -10.7 – -4.4), -4.4 (95% CI = -6.9 – -2.0), and -7.1 (95% CI = -10.7 – -3.5) ms/mmHg, respectively. After adjusting for sex, the regression coefficients were -6.9 (95% CI = -10.0 – -3.8), -3.5 (95% CI = -5.9 – -1.1) and -6.2 (95% CI = -9.8 – -2.6) ms/mmHg, respectively.

Median dHR/dSBP was 1.01 (IQR = 0.75 – 1.36) in younger adults and 0.53 (IQR = 0.39 – 0.91) in older adults.

Standing up from sitting versus supine position

Table 10.2 lists the differences in BP drop amplitude and cerebral oxygenation drop and recovery amplitude between standing up from supine and sitting position. Initial O_2Hb drop amplitude after standing up from supine position was significantly larger compared to standing up from sitting position in both younger (Δ = 2.96 µmol/L, $p < 0.001$) and older (Δ = 0.89 µmol/L, $p = 0.036$) adults.

Test-retest reliability

The range of O_2Hb and HHb drop and recovery amplitude ICCs was 0.05 – 0.67 (sit to stand) and 0.68 – 0.94 (supine to stand). The range of O_2Hb recovery time ICCs was -0.11 – -0.032 (sit to stand) and 0.095 – 0.49 (supine to stand). BRS ICCs ranged between 0.49 to 0.86 (supine rest), 0.34 to 0.35 (sit to stand) and 0.55 to 0.83 (supine to stand).

Discussion

In this study assessing cerebral oxygenation and baroreflex sensitivity during postural change as potentially useful measures of compensatory mechanisms in orthostatic hypotension, oxygenated and deoxygenated hemoglobin drop amplitude were unexpectedly smaller in older adults compared to younger adults; oxygenated hemoglobin recovery was slower and baroreflex sensitivity (BRS) was lower. Standing up from supine position evoked a larger oxygenated hemoglobin drop compared to standing up from sitting position. The test retest-reliability results indicated the robustness of the measurements, particularly during standing up from supine position.

The first aim of the study was to assess the association between measures of orthostatic cerebral oxygenation and age. Orthostatic cerebral oxygenation drop amplitude was larger in younger adults compared to older adults, which was not in line with the hypothesis and two previous studies.[11,13] The finding may indicate that younger adult brains tolerates larger drops in cerebral oxygenation compared to older adult brains as they typically have a higher baseline cerebral blood flow and cerebral oxygenation.[24,25] Older adults may consequently be more vulnerable for drops in cerebral blood flow and cerebral oxygenation, requiring a larger compensating role

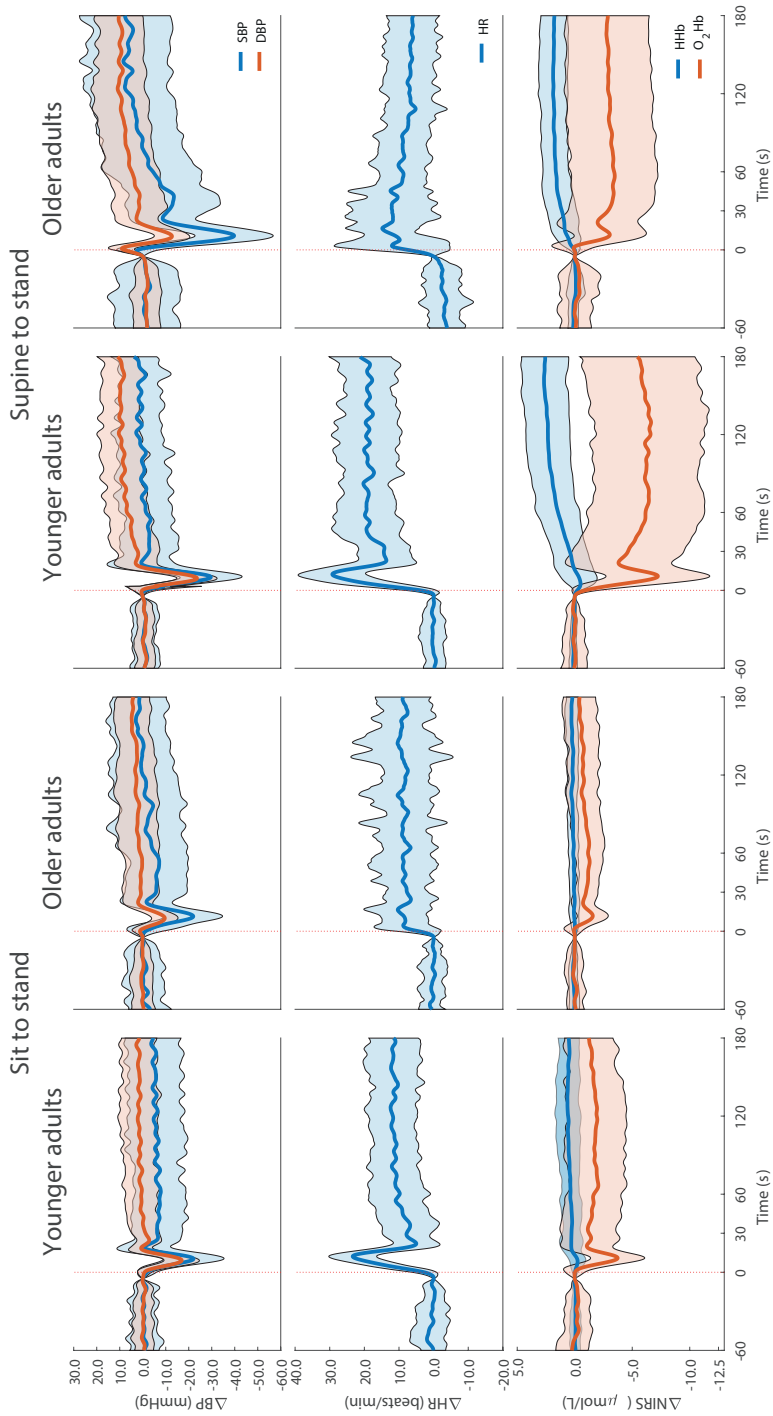

Figure 10.1. Blood pressure (BP), heart rate (HR) and cerebral oxygenation measured using near infrared spectroscopy (NIRS) during sit to stand and supine to stand maneuvers in younger and older adults All signals are unfiltered and baseline (mean of 60 seconds before standing up) is subtracted. The red vertical line indicates the onset of standing up. The shaded areas indicate the standard deviation. SBP: systolic blood pressure; DBP: diastolic blood pressure; O_2Hb: oxygenated hemoglobin; HHb: deoxygenated hemoglobin.

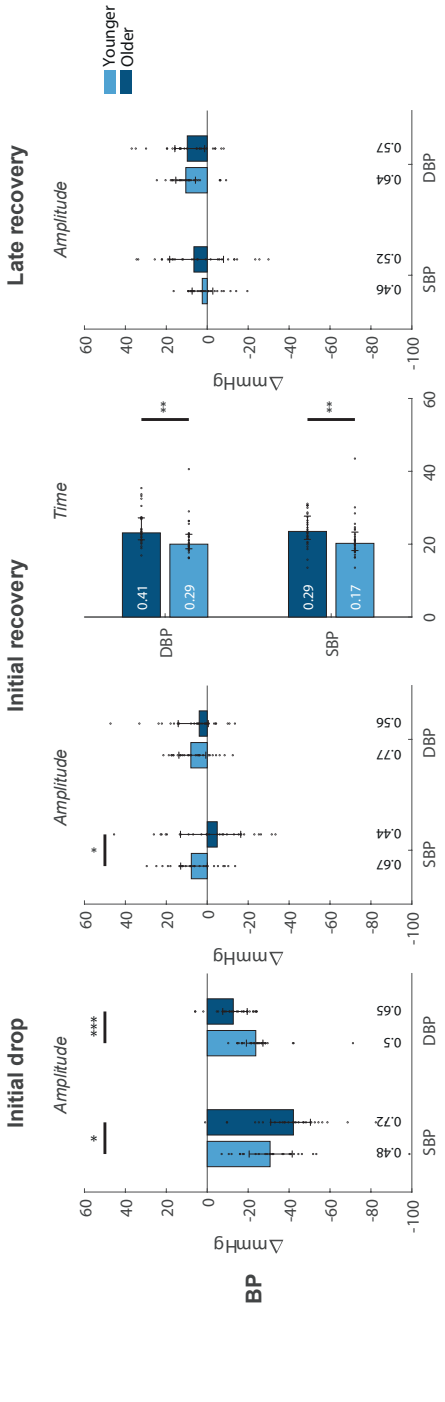

Figure 10.2. Initial drop and initial and late recovery of blood pressure (top panels) and cerebral oxygenation (bottom panels) after standing up from supine position in younger and older adults. The error bars indicate the inter quartile range and dots the separate data points. The reliability is expressed as intra class correlation at the base of each bar. The stars indicate statistical significant differences between younger and older adults (one, two and three stars indicating $p < 0.05$, < 0.01, and < 0.001, respectively). SBP: systolic blood pressure; DBP: diastolic blood pressure; O_2Hb: oxygenated hemoglobin; HHb: deoxygenated hemoglobin.

Table 10.2. Difference in BP drop and cerebral oxygenation drop and recovery amplitude between types of postural change

		Younger adults			Older adults	
	N	Difference	P-value	N	Difference	P-value
Blood pressure						
Initial SBP drop amp., ΔmmHg, median [IQR]	25	6.98 [0.02 – 10.11]	0.051	28	13.6 [3.94 – 21.3]	**< 0.001**
Initial DBP drop amp., ΔmmHg, median [IQR]	25	4.17 [1.55 – 8.24]	**0.003**	28	1.97 [-1.28 – 7.25]	0.053
Cerebral oxygenation						
Drop						
Initial O_2Hb drop amp., Δμmol/L, median [IQR]	24	2.96 [1.43 – 6.33]	**< 0.001**	26	0.89 [-0.67 – 3.55]	**0.036**
Initial HHb drop amp., Δμmol/L, median [IQR]	24	0.36 [-0.32 – 1.24]	**0.048**	26	-0.23 [-0.75 – 0.20]	0.091
Recovery						
Initial O_2Hb recovery amp., Δμmol/L, median [IQR]	25	2.97 [-0.09 – 5.83]	**0.002**	26	1.02 [-0.91 – 3.06]	0.073
Initial HHb recovery amp., Δμmol/L, median [IQR]	25	0.13 [-0.51 – 1.30]	0.253	26	-1.26 [-2.00 – -0.45]	**< 0.001**
Late O_2Hb recovery amp., Δμmol/L, median [IQR]	25	4.78 [0.44 – 7.56]	**< 0.001**	26	1.44 [-0.32 – 3.58]	**0.009**
Late HHb recovery amp., Δμmol/L, median [IQR]	25	-1.47 [-2.45 – -4.02]	**< 0.001**	26	-1.80 [-2.30 – -1.17]	**< 0.001**

Cerebral oxygenation drop and recovery differences were computed by subtracting their value computed during standing up from supine position form their value computed during standing up from sitting position. Bold-printed p-values represent statistically significant differences from zero as tested using the Wilcoxon signed rank test. Amp: amplitude; IQR: inter quartile range.

of cerebral autoregulation. The results of the present study suggest that cerebral autoregulation in older adults is able to limit the magnitude of cerebral oxygenation drop. Alternatively, the relatively high arterial and venous compliance in younger adults may partly explain the results as this facilitates the pooling of blood in the legs, orthostatic BP drop and potentially cerebral oxygenation.[26–28] Discrepancies between findings of the present and aformentioned studies may be explained by use of different age criteria[11] and postural changes (active versus passive).[13]

The estimation of differential pathway factor (DPF) is important as it is used to compute changes in cerebral oxygenation levels in individuals.[29] Assumptions for this estimation in the present study may explain part of the found orthostatic cerebral oxygenation differences between younger and older adults. However, inaccurate estimation of DPF based on the Scholkmann formula is unlikely to fully explain the differences between the groups as demonstrated in supplementary file S10.1.

The finding that initial cerebral oxygenation recovery was delayed in older adults compared to young adults suggests a slower activity of cerbral autoregulation in older adults.[30] The relationship between cerebral oxygenation and autoregulation should be further investigated in studies simultaneously measuring BP, NIRS and transcranial doppler ultrasound (TCD) as TCD enables the measurement of absolute cerebral blood flow velocity in contrast to NIRS, which measures changes of oxygenated and deoxygenated hemoglobin relative to an unknown baseline.

The second aim of the study was to assess the association between BRS and age. BRS was lower in older adults compared to younger adults during both types of

postural changes, which was in line with the hypothesis and potentially indicates that older adults are more vulnerable for orthostatic hypotension. The dHR/dSBP ratio lower than 0.5 in approximately half of the older adults suggests impaired function of the afferent or efferent neural baroreflex pathways.[21,31,32] The increased arterial vessel stiffness associated with age may further impair baroreceptor stretch and hence baroreflex function.[33,34] Adjusting the found association between age and BRS for sex lowered the effect size, indicating a partial confounding role of sex.

The third aim of this study was to assess the influence of the type of postural change on orthostatic cerebral oxygenation. Cerebral oxygenation drop after standing up from supine position was larger compared to standing up from sitting position, which seems to reflect the magnitude of the orthostatic challenge and the consequent pooling of blood in the legs. This is also suggested by the significantly larger BP drop after standing up from supine position in both younger and older adults. The difference between oxygenated hemoglobin drop between the conditions was smaller in older adults compared to young adults, supporting the idea that orthostatic cerebral oxygenation drops particularly need to be limited in the older adult brain.

The test-retest reliability results indicate that NIRS-derived cereberal oxygenation amplitude measures and BRS measures assessed during standing up from supine position are robust (good to excellent test-retest reliability), suggesting these measures to be potentially clinically applicable in individuals. However, NIRS-derived cereberal oxygenation amplitude measures assessed during sit to stand condition and cerebral oxygenation time measures had fair or poor robustness.

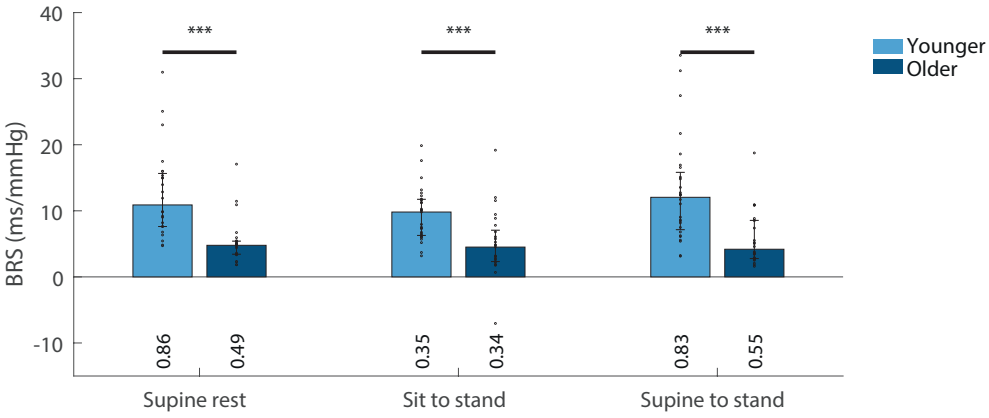

Figure 10.3. Baroreflex sensitivity (BRS) at during supine rest and standing up in younger and older adults. Error bars indicate the inter quartile range. Dots indicate data points corresponding to individual participants. Test-retest reliability expressed as intra class correlations are shown below the bars.

Strength and limitations

The strength of this study is that it systematically assessed the differences in orthostatic cerebral oxygenation and baroreflex sensitivity between younger and older adults and between two relevant types of postural changes. Limitations of this study include the difference in sex distribution between the age groups and the absence of cerebral blood flow measurements.

Conclusion and future directions

Cerebral oxygenation drop after postural change was smaller and recovered slower in older adults compared to younger adults, suggesting that cerebral autoregulation in older adults is able to mitigate oxygenation drops, but responds slower. Older adults may be more vulnerable for orthostatic hypotension compared to younger adults as they had a lower orthostatic baroreflex sensitivity. The orthostatic challenge posed to cerebral autoregulation was suggested to be larger after standing up from supine position compared to sitting position by the orthostatic cerebral oxygenation results. Cerebral oxygenation amplitude and BRS measures during standing up from supine position were found to be robust, further indicating their potential use in studies on the clinical implications of orthostatic hypotension.

Further studies should more directly address the role of cerebral autoregulation by simultaneously measuring TCD and determine clinical relevance of the investigated cerebral oxygenation and baroreflex sensitivity measures by addressing their association with clinical outcome in patients with orthostatic hypotension.

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Supplementary file S10.1

Demonstration of the potential effect of differential pathway factor on the found results

According to the Lambert-Beer law, $\Delta c = \Delta OD_{\lambda} / (\varepsilon_{\lambda} * L * DPF)$; where c signifies cerebral (de)oxygenated hemoglobin concentration; OD optical density, i.e., the logarithm of the incident divided by the reflected light; epsilon the extinction coefficient of the chromophore (O_2Hb or HHb); and L the straight distance between transmitter and receiver, all at a specific wavelength of incident light, lambda. DPF signifies the factor by which the travelled light from NIRS transmitter to NIRS receiver is longer than the straight distance due to scattering, and is dependent on the tissue properties and age. DPF is generally estimated based on age using the Scholkmann formula: $DPF = a + b*age^{c}$, where a, b and c are positive constants depending on wavelength.[17] The Scholkmann formula is validated for ages between 0 and 50 years. In the present study, the value corresponding to 50 years was used in all adults aged above 50 years, thereby potentially overestimating concentration changes in these individuals. However, for the wavelengths used by the NIRS devices, the DPF difference between 50 years (the assumed age) and 77 years (the median age in chapter 10) is approximately 10%,[17] while the difference in concentration changes between the age groups is 100-200%.

Chapter 11

Cerebral autoregulation assessed by near-infrared spectroscopy: validation using transcranial Doppler in patients with controlled hypertension, cognitive impairment and controls

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Submitted

Abstract

Background: Cerebral autoregulation (CA) aims to attenuate the effects of blood pressure variation (e.g. during orthostatic hypotension) on cerebral blood flow and oxygenation. The gold standard to assess dynamic CA is the combination of transcranial Doppler (TCD) and continuous blood pressure measurements, but TCD has limitations due to insonation window requirements and poor patient friendliness. This study assessed the criterion validity of CA derived from near-infrared spectroscopy (NIRS) as alternative for TCD.

Methods: Measurements of continuous blood pressure (BP), oxygenated hemoglobin (O_2Hb) using NIRS and cerebral blood flow velocity (CBFV) using TCD (gold standard) were performed in 54 younger controls, 28 older controls, 27 patients with hypertension and 94 cognitively impaired patients during 5 minutes of supine rest (all individuals) and 5 minutes of repeated sit to stand transitions (cognitively impaired patients). The BP-CBFV and BP-O_2Hb transfer function phase shifts (TF_φ) were computed, corrected for effects arising from the cerebral microvasculature (only BP-O_2Hb), and averaged in the very low (VLF, 0.02-0.07Hz) and low (LF, 0.07-0.2Hz) frequency ranges as CA measures. Spearman correlations and Bland Altman 95% limits of agreement (BAloa) between NIRS- and TCD-derived CA measures were computed. BAloa separation < 50 degrees was used as a criterion for clinical applicability in individuals.

Results: NIRS- and TCD-derived CA estimates were significantly correlated during supine rest ($\rho = 0.22 – 0.30$, $N = 111 – 120$) and repeated sit to stand transitions ($\rho = 0.46 – 0.61$, $N = 19 – 32$). BAloa separation ranged between 87 – 112 degrees (supine rest) and 65 – 77 degrees (repeated sit to stand transitions).

Conclusions: The results suggest NIRS-derived CA estimates to be criterion valid on group level, but insufficient for clinical application in individuals.

Introduction

Cerebral autoregulation (CA) is the vascular mechanism aiming to keep cerebral blood flow constant during blood pressure (BP) fluctuations by constricting or dilating cerebral arterioles in response to BP increases and decreases, respectively.[1,2] Static and dynamic CA are distinguished to express the ability of CA to maintain cerebral blood flow during a changed steady state BP and fluctuating BP, respectively.[3,4] Dynamic CA function is dependent on the frequency and speed of BP changes and can in contrast to static CA not be measured using MRI, PET or SPECT.[3,4] Impaired dynamic CA was reported in patients with stroke and traumatic brain injury[5,6] and may be a risk factor for mild cognitive impairment (MCI) and dementia, particularly in patients with hypertension and orthostatic hypotension.[7–9] Presently, dynamic CA is usually assessed using Transcranial Doppler (TCD) measurements, which provide

a valid approximation of cerebral blood flow measured using MRI.[10] However, TCD measurements require skilled investigators, do not allow for longer recordings, and are not feasible in a substantial proportion of older adults due to temporal bone abnormalities, limiting TCD availability and applicability in clinical populations.[2,11]

Near infrared spectroscopy (NIRS) is a potential alternative for TCD and measures changes in cerebral oxygenated and deoxygenated hemoglobin concentrations by detecting the intensity of reflected light emitted into the brain. NIRS measurements were suggested to be potentially useful to assess CA in healthy young individuals,[12–14] healthy older adults,[15] and various clinical populations.[16–18] NIRS-derived CA estimation may be performed using the cerebral oximetry index, or transfer function analysis (TFA) phase shift correcting for effects arising from the cerebral microcirculation using information in the high frequency range (0.2 – 0.5 Hz), in which CA is not active.[13,19] However, there is very limited evidence on the validity of NIRS-derived CA estimation in an older, clinical population, for example with chronic diseases such as hypertension and cognitive impairment.

In this study, we assessed the criterion validity of NIRS-derived CA estimation in younger and older controls, patients with controlled hypertension, mild cognitive impairment (MCI) and Alzheimer's dementia (AD) during supine rest and repeated sit to stand transitions. We hypothesize that NIRS-derived CA estimates correlate with TCD-derived CA measures, and have high absolute agreement, i.e., a separation between upper and lower 95% limits of agreement < 50 degrees.[20]

Methods

Study cohorts

BP, TCD and NIRS data from six cohorts, collected between 2008 and 2018 at three different centers, were included in this study: two cohorts of younger adults (younger controls; n = 39 and 14; mean age < 65 years), a cohort of older adults (older controls; n = 28; mean age > 65 years), a cohort of patients with controlled hypertension (n = 27), and cohorts of patients with MCI and AD (cognitively impaired patients; n = 37 and 57). The centers were 1) the Department of Neurology, Lucerne Kantonsspital, Lucerne, Switzerland (younger controls cohort 1 and patients with controlled hypertension); 2) the University Groningen Medical Center, Groningen, the Netherlands (younger controls cohort 2); 3) the Radboud University Medical Center, Nijmegen, the Netherlands (older controls and patients with MCI and AD). Table 11.1 lists the inclusion and exclusion criteria per cohort.

In the quantitative analysis, data from the two cohorts of younger controls and patients with MCI and AD were pooled, leaving four pooled cohorts for statistical analysis: younger controls, older controls, hypertension patients and cognitively impaired patients.

Table 11.1: Cohort characteristics

	Younger controls (cohort 1)	Younger controls (cohort 2)	Older controls	Patients with controlled hypertension	MCI patients	AD patients
Inclusion						
N	39	14	28	27	37	57
Measurement site	Luzerner Kantons-spital[1]	UMCG[2]	Radboudumc[3]	Lucerne Kantonsspital[1]	Radboudumc[3]	Radboud-umc[3]
Inclusion / exclusion criteria	- no smoking - absence of any medical conditions	- Age between 20-50 years - Absence of any medical conditions	- Age > 50 years - no medical history of cardiovascular or cerebrovascular disease - not using cardiovascular or psychotropic medication	- patients referred for diagnosis of cerebro-vascular diseases - history of SBP > 140 and/or DBP > 90 for > 2 years, successfully treated - no more than 50% stenosis of large arteries on duplex US. - no smoking - no cardiac arrhythmias or heart failure	- Age > 50 years - Clinical diagnosis of MCI due to AD according to the NIA-AA criteria - MOCA score 18 - 26.	- Age > 50 years - Clinical diagnosis of AD according to the NIA-AA criteria - MMSE score between 12 - 26
Data collection						
BP device	Finometer Pro[4]	Portapres[4]	Finometer Pro[4]	Finometer Pro[4]	Finometer Pro[4]	Finometer Pro[4]
TCD device (sampling frequency)	Multidop[5] (2 MHz)	Delica[6] (2 MHz)	Multidop[5] (2 MHz)	Multidop[5] (2 MHz)	Doppler-BoxX[5] (2 MHz)	Multidop[5] (2 MHz)
NIRS device (sampling frequency)	NIRO-200NX[7] (5 Hz)	Portalite[8] (50 Hz)	Oxymon Mk III[7] (10 Hz)	NIRO-200NX[7] (5 Hz)	Oxymon Mk III[8] (10 Hz)	Oxymon Mk III[8] (10 Hz)
NIRS wavelengths	735, 810 and 850 nm	760 and 850 nm	765, 857 and 859 nm	735, 810 and 850 nm	765, 857 and 859 nm	765, 857 and 859 nm
NIRS inter optode distance	4 cm	4.0 cm	5 cm	4 cm	5 cm	5 cm

MCI: mild cognitive impairment; AD: Alzheimer's dementia; BP: blood pressure; TCD: Transcranial Doppler; NIRS: near-infrared spectroscopy; SBP: systolic blood pressure; DBP: diastolic blood pressure; US: ultrasound; MOCA: Montreal Cognitive Assessment; MMSE: Mini Mental State Examination; [1]Department of Neurology, Lucerne Kantonsspital, Lucerne, Switzerland; [2] University Medical Center Groningen, Groningen, the Netherlands; [3]Radboud University Medical Center, Nijmegen, the Netherlands; [4]Finapres Medical Systems, Amsterdam, The Netherlands; [5]Compumedics DWL, Singen, Germany; [6]Shenzhen, China; [7]Hasamotu Photonics, Herrsching, Germany; [8]Artinis Medical Systems, Elst, The Netherlands

Table 11.2: Characteristics of patients and controls

Characteristic	Younger controls (cohort 1; N=39)		Younger controls (cohort 2; N=14)		Older controls (N=28)		Patients with controlled hypertension (N=27)		MCI patients (N=37)		AD patients (N=57)	
Age, years, mean (SD/range)	39	48.0 (17.7)	14	28 (21-45)	28	70.0 (3.7)	27	67.0 (14.7)	37	69.2 (8.4)	57	73.3 (6.1)
Female, n (%)	39	17 (43.6)	14	11 (78.6)	28	12 (42.9)	27	18.5	37	12 (32.4)	57	32 (56.1)
BMI, kg/m^2, mean (SD)	39	< 30		NA	28	26.2 (2.9)	27	< 30	37	26.0 (3.7)	57	24.8 (3.7)
Current smoking, n (%)	39	0 (0)		NA		NA	27	0 (0)	31	4 (12.9)		NA
Cardiovascular or cerebrovascular disease, n (%)	39	0 (0)	14	0 (0)	28	0 (0)	27	27 (100)	30	9 (30.0)	57	43 (75.4)
Cardiovascular or psychotropic medication, n (%)	39	0 (0)	14	0 (0)	28	0 (0)	27	27 (100)	19	13 (68.4)	57	16 (28.1)
MMSE, points, median [IQR]		NA		NA	28	29 [28 – 30]		NA		NA	57	16.9 (3.3)
MOCA, points, median [IQR]		NA		NA		NA		NA	37	23 [20.5-25]		NA
SBP, mmHg, mean (SD)	39	113.8 (16.6)[1]	14	129.8 (21.8)[1]	28	132.9 (12.8)[2]	26	124.0 (15.6)[1]	37	142.8 (22.0)[2]	57	138 (13.1)[2]
DBP, mmHg, mean (SD)	39	68.4 (12.1)[1]	14	79.4 (18.2)[1]	28	78.5 (9.6)[2]	26	67.5 (12.9)[1]	37	83.8 (12.2)[2]	57	78.4 (6.4)[2]
Cerebral blood flow velocity, cm/s, mean (SD)	39	62.8 (13.6)	14	62.3 (8.7)	23	46.0 (8.8)	26	53.2 (12.8)	33	41.8 (12.3)	39	38.2 (9.6)

The table lists patient characteristics for each of the included cohorts. SD: standard deviation; IQR: interquartile range; BMI: Body Mass Index; MMSE: mini mental state examination; MOCA: Montreal cognitive assessment; HR: Heart rate; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; CBFV: cerebral blood flow velocity; VLF: very low frequency range; LF: low frequency range; HF: high frequency range; MCI: mild cognitive impairment; AD: Alzheimer's dementia; BP: blood pressure. [1]Measured using continuous BP monitor. [2]Measured using a sphygmomanometer

All patients and controls signed informed consent and for all studies medical ethical approval was obtained and they were performed in accordance with the declaration of Helsinki.

Participant characteristics

Information about age, sex, smoking habits, medical history and use of medication were obtained. Body mass index (BMI) and cognitive performance (MMSE and/or MOCA) were measured in older controls and patients with MCI and AD.

Instrumentation

Blood pressure (BP), near-infrared spectroscopy (NIRS) and transcranial Doppler (TCD) were simultaneously measured. The used BP, TCD and NIRS devices and manufacturers per cohort are listed in Table 11.1 as well as the used sampling frequencies, wavelengths and inter optode distances.

Continuous, beat-to-beat BP was measured non-invasively using finger photoplethysmography. Near-infrared spectroscopy (NIRS) measurements were obtained bilaterally on the forehead to assess changes in cerebral oxygenated hemoglobin concentrations (O_2Hb). The differential pathway factor (DPF), which accounts for the increased distance traveled by light due to scattering, is age-dependent and was computed using the following formula in adults aged below 50 years[21]: $4.99 + 0.067 \times Age^{0.814}$. In other individuals DPF was set to 6.61, the value for an age of 50 years, the highest age for which the formula is validated. Transcranial Doppler (TCD) measurements were performed bilaterally over the temporal bone to measure cerebral blood flow velocity (CBFV) in the middle cerebral arteries. The TCD probes were fixed using a head holder.

Protocol

Room temperatures between 20 and 23 degrees Celsius were pursued. Patients and controls were discouraged from talking and moving during the measurements.

Patients were asked to lie supine for at least 5 minutes during which blood pressure, cerebral blood flow velocity and oxygenated and deoxygenated cerebral hemoglobin (O_2Hb and HHb, respectively) were measured.

Measurements during repeated sit to stand transitions were performed in patients with MCI and AD. The seat was adjusted to the patient's height. Patients were asked to switch from sitting and standing position every 10 seconds (full cycle period of 20 seconds; frequency of 0.05 Hz) during 5 minutes to induce BP, CBFV and O_2Hb oscillations.

Data analysis

All analysis was performed using MATLAB (version R2019b, The MathWorks Inc., Natick, Massachusetts, USA).

Signal preprocessing
All signals were resampled to a uniform sampling frequency of 200 Hz and a moving median filter with a 0.15 second window was applied to remove spike artefacts from the signals.

Signal quality assessment
The quality of BP, CBFV and O_2Hb signals was visually assessed by two authors (AM and JWE). This was performed separately for each signal, individual, side (left/right) and test condition. A signal was considered poor quality and discarded if it contained spike or step artefacts, or a recurrent heart beat was not visible.

Transfer function analysis (TFA)
BP-CBFV (TCD-derived) and BP-O_2Hb (NIRS-derived) transfer functions (TF) were computed for both sides in each individual using software from the CARNet community.[2] Signals were filtered using a 6th order Butterworth lowpass filter with a cutoff of 0.5 Hz and the signal mean was subtracted before performing the TFA. TF gain (TF_g), phase shift (TF_φ) and coherence (TF_c) were computed as a function of frequency. TF_g and TF_φ with insignificant coherence in a frequency bin (tested according to the CARNet recommendations)[2] were discarded from further analysis.

TF_φs were averaged over the sides with available data per individual and subsequently averaged over individuals to obtain grand average TF_φs per cohort. Averaging was performed using the circular mean. NIRS and TCD-derived grand average TF_φs were plotted together to enable visual assessment of their differences.

The very low frequency (VLF), low frequency (LF) and high frequency (HF) ranges were defined as 0.02 – 0.07 Hz, 0.07 – 0.2 Hz and 0.2 – 0.5 Hz, respectively.[13] Mean TF_φ in the VLF and LF ranges were used as CA measures.

Correction for cerebral microcirculation effects
The BP-O_2Hb TF_φs were corrected for cerebral microcirculation effects on waveform morphology: CBFV waveforms typically have a steeper upstroke compared to O_2Hb waveforms, resulting in a relatively constant negative phase shift across frequencies (demonstrated in Supplementary File S11.1). Correction was performed by computing the mean phase shift in the HF range (in which CA is not active) and subtracting this mean phase shift from the TF_φ (Figure 11.1). The HF range mean phase shift was determined based on the pooled cohort average TF_φ.

Statistical analysis
Circular means and standard deviations were used to aggregate phase shift data.

TF_φs were consecutively averaged over sides (left/right) and over frequencies within frequency ranges (VLF and LF), resulting in mean VLF and LF TF_φs for each individual.

Spearman rank correlations of NIRS- and TCD-derived CA estimates were

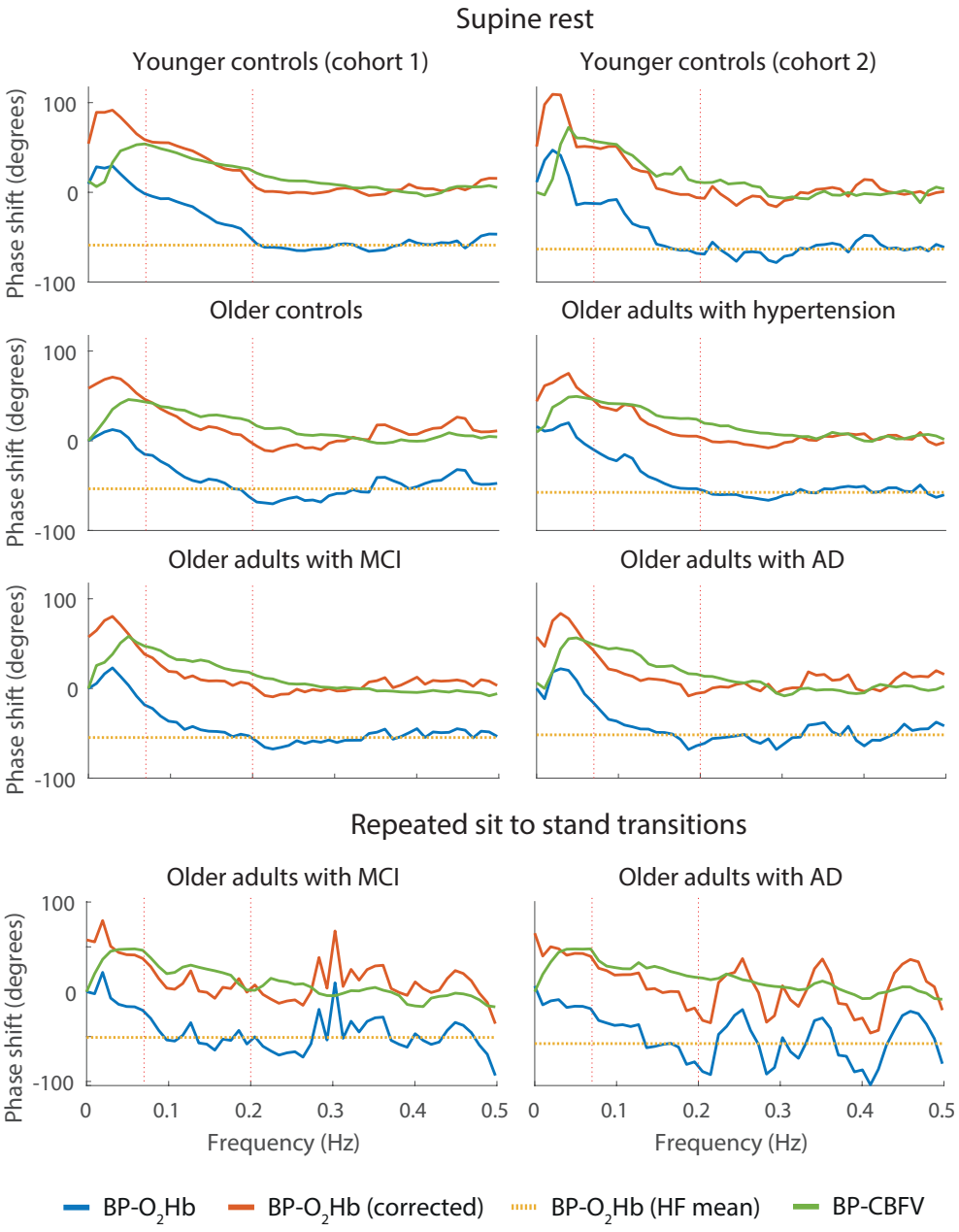

Figure 11.1. Grand average of BP-CBFV and BP-O2Hb TF_φ in supine rest and during repeated sit to stand transitions, per cohort. The blue and red traces are the BP-O2Hb TF_φs before and after correction, respectively. The yellow dotted lines are the means lines of the BP-O2Hb TF_φ in the high frequency (HF) range. MCI: mild cognitive impairment; AD: Alzheimer's dementia.

Table 11.3: Cerebral autoregulation estimates derived from TCD and NIRS

	Supine rest										Sit to stand transitions	
	Younger controls (N=53)		Older controls (N=28)		Hyper-tension patients (N = 27)		Cognitively impaired patients (N=94)		All (N=202)		Cognitively impaired patients (N=94)	
BP-CBFV and BP-O_2Hb												
VLF												
GA error bc, mean (SD), degrees[1]	39[2]	-40 (20)	17[2]	-42 (13)	18[2]	-41 (12)	46[2]	-46 (17)	120[2]	-43 (16)	32[2]	-62 (5)
GA error ac, mean (SD), degrees[1]	39[2]	23 (20)	17[2]	18 (12)	18[2]	14 (11)	46[2]	12 (17)	120[2]	16 (16)	32[2]	-4 (5)
Spearman correlation	39	0.00	17	0.24	18	0.55*	46	0.24	120	0.22*	32	0.46**
BA bias (loa), degrees	39	24 (149)	17	16 (65)	18	13 (82)	46	7 (91)	120	14 (112)	32	-0 (78)
LF												
GA error bc, mean (SD), degrees[1]	36[2]	-65 (7)	15[2]	-72 (7)	17[2]	-69 (8)	46[2]	-76 (13)	111[2]	-71 (4)	19[2]	-75 (7)
GA error ac, mean (SD), degrees[1]	36[2]	-2 (7)	15[2]	-12 (6)	17[2]	-12 (7)	46[2]	-19 (13)	111[2]	-12 (3)	19[2]	-17 (7)
Spearman correlation	36	0.37*	15	0.16	17	-0.06	43	0.30	111	0.30**	19	0.62**
BA bias (loa), degrees	36	2 (109)	15	-10 (52)	17	-2 (73)	43	-11 (71)	111	-5 (86)	19	-4 (65)

Grand average (GA) errors before and after correction (bc and ac, respectively), and Spearman correlations and Bland Altman (BA) analysis results between NIRS- and TCD-derived CA measures within groups. BP: blood pressure; CBFV: cerebral blood flow velocity; O_2Hb: oxygenated hemoglobin; loa: separation between 95% upper and lower limits of agreement. One and two stars indicate statistically significant correlations with p values lower than 0.05 and 0.01, respectively. [1]Mean and standard deviation over frequencies within frequency range; [2]Represents the number of patients for whom both BP-CBFV and BP-O_2Hb TFs was available. The number of patients for whom the separate TFs were available (enabling them to be included in the TF grand average) was higher (see Supplementary Table S11.2).

computed as a measure of criterion validity. Furthermore, the absolute difference between NIRS- and TCD derived CA estimates were visualized using Bland Altman plots and 95% upper and lower limits of agreement were computed. A separation between upper and lower limits of agreement < 50 was considered high absolute agreement.[20] This value corresponds to the separation between 95% limits of agreement of Bland Altman analysis reflecting the test-retest reliability of TCD-derived CA measures.[20]

P-values < 0.05 were considered statistically significant.

Results

Table 11.2 lists the participant characteristics per cohort. During supine rest, each signal (BP, CBFV, O_2Hb) was available in good quality in 148/202 patients (73.2%; younger controls: 26/41; older controls 19/28; hypertension patients: 23/27; cognitively impaired patients: 59/94). During the repeated sit to stand transitions, each signal was available in good quality in 35/94 cognitively impaired patients (37.2%).

Figure 11.1 shows the grand average BP-CBFV and BP-O_2Hb TF_φs both in supine rest and during repeated sit to stand transitions. After correction, the grand average BP-O_2Hb TF_φ approximates the BP-CBFV TF_φ in all cohorts and both test conditions on inspection, in the VLF range. Errors before and after correction are listed in Table 11.3.

Table 11.3 further lists the correlations between NIRS- and TCD-derived CA estimates in the entire population as well as the different pooled cohorts. Supplementary Table S2 lists the mean TF_g, TF_φ and TF_c for each pooled cohort, test condition, TF, and frequency range. During supine rest, Spearman correlations between NIRS- and TCD- CA measures were 0.22 (n = 120, p = 0.016) and 0.30 (n = 111, p = 0.002) for the VLF and LF range, respectively. In the pooled cohorts, Spearman correlations were only significant in patients with hypertension (VLF) and younger controls (LF). During repeated sit to stand transitions in cognitively impaired patients, Spearman correlations were 0.46 (n = 32, p = 0.009) and 0.61 (n = 19, p < 0.001), respectively.

Figure 11.2 shows the Bland Altman plots of the differences between NIRS- and TCD-derived CA estimates within the entire population of all patients and controls and Table 11.3 lists the Bland Altman bias and 95% limits of agreement separation per pooled cohort. For measurements in supine rest, the 95% limits of agreement were -42 – 70 degrees (VLF) and -49 – 38 degrees (LF). For measurements during repeated sit to stand transitions, the 95% limits of agreement were -39 – 38 degrees (VLF) and -37 – 28 degrees (LF).

Discussion

This study assessed the criterion validity of near-infrared spectroscopy (NIRS) as a cerebral autoregulation (CA) estimation method in 202 younger and older controls, older adults with controlled hypertension and patients with cognitive impairment during supine rest and repeated sit to stand conditions using transcranial Doppler (TCD) as a gold standard. Correction of NIRS-derived CA estimates for waveform morphology differences between CBFV and O_2Hb signals reduced the errors in the grand average. Significant but low correlations (0.22 – 0.30) between NIRS and TCD-derived CA measures were found for measurements performed during supine rest. During repeated sit to stand transitions, correlations were higher (0.46 – 0.61), but the analyzed number of individuals was low (19 – 32). Bland Altman analyses showed a low absolute agreement between NIRS- and TCD-derived CA measures (separation between upper and lower 95% limits of agreement ranging from 65 – 112 degrees).

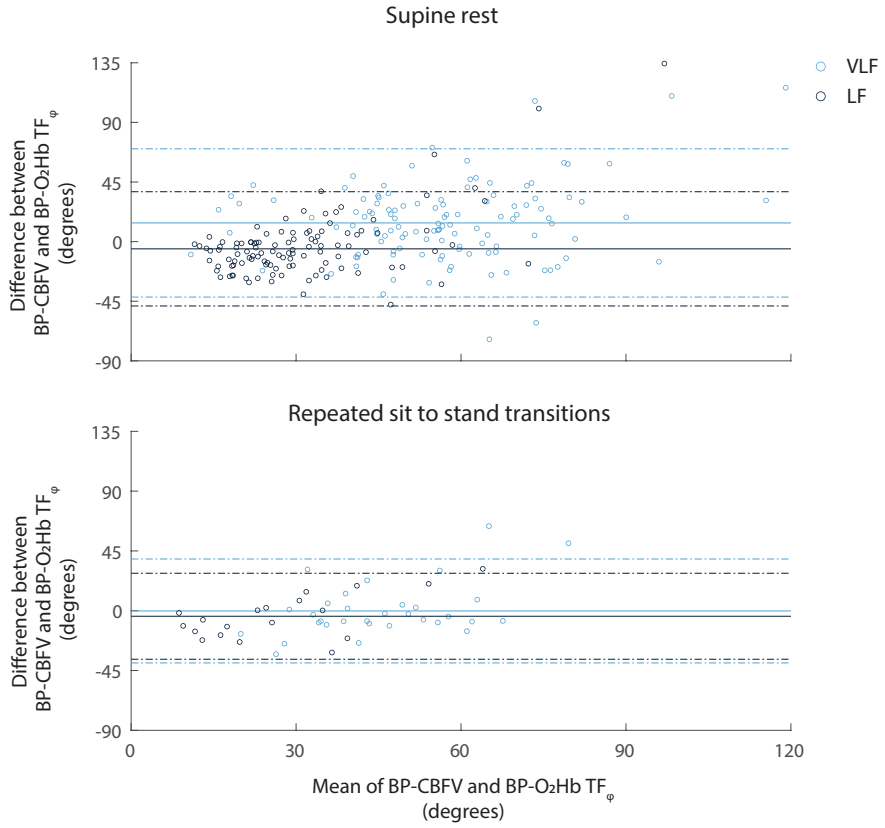

Figure 11.2. Bland Altman plots showing agreement between NIRS- and TCD- derived CA measures during supine rest and repeated sit to stand transitions. The horizontal solid lines indicates the mean difference; the horizontal dashed lines indicate the 95% limits of agreement. VLF: very low frequency range; LF: low frequency

Correction of the BP-O_2Hb TF_φ by subtracting the negative mean phase in the HF range contributed to CA estimation validity both during supine rest and repeated sit to stand transitions as indicated by the lower grand average errors after correction. This negative mean phase was shown to reflect waveform morphology differences that may arise as a result of differences in microvascular resistance profiles and perfusion pressures between the systemic and cerebral circulations.

The significant correlations between NIRS- and TCD-derived CA measures suggest that NIRS-derived CA estimates may be used to compare groups. Absolute differences between NIRS and TCD-derived CA measures in individuals were higher than the cutoff criterion, which was based on the TCD derived CA test-retest reliability.[20] This indicates that NIRS- derived CA estimation in individuals in its current form has insufficient validity for clinical application.

The correlation between NIRS- and TCD- derived CA measures was particularly large when measured during repeated sit to stand transitions. The transitions increased the coherence between BP, CBFV and O_2Hb in the VLF range, implying a better validity of the TFA linearity assumption.[2] The relatively high correlation between NIRS- and TCD-derived CA measures during repeated sit to stand transitions may also be explained by the higher BP variability, which was reported to be a positive determinant of CA reliability in a previous study.[22] Previous studies suggested the particular clinical manifestation of poor CA during and after transitions as these may challenge CA beyond its capacity by eliciting orthostatic hypotension.[23–26] However, the number of individuals with good quality signals during sit to stand transitions in the present study was low.

The correlation between NIRS- and TCD-derived CA measures was higher in the LF range compared to the VLF range. Non-linear behavior in the VLF range may play a role as reported in a previous study and indicated by the low coherence in the VLF range compared to the LF and HF range.[27] As demonstrated in supplementary file S11.1, estimation of the CBFV-O_2Hb TF_φ using the HF mean of the BP-O_2Hb TF_φ was less accurate in the VLF compared to the LF range. The findings may also be explained by the relatively short duration of the measurements relative to the oscillation period in the VLF range, implying a potentially large effect of artefacts on the BP-O_2Hb TF_φ in this frequency range. Further studies should preferably prolong the measurements, which is feasible with NIRS, though challenging with TCD. Longer measurements enable the selection of data segments with more BP variation, improving the reproducibility of CA assessment.[22]

The correlation between NIRS- and TCD- derived CA measures was significant in the entire population of patients and controls during supine rest, but not in each of the pooled cohorts. Apart from low sample sizes, device and data quality differences between the different centers may have played a role. For example, differences in NIRS inter optode distance (i.e., the distance between transmitter and receiver),

which partly determines the volume of brain tissue being sampled, may have influenced the results.[28] Which inter optode distance is to be preferred needs to be addressed further studies.

A considerable proportion the included individuals did not have an adequate quality of all signals (BP, CBFV, O_2Hb) during supine rest, which is a limitation of this study. The proportion was lowest (62.7%) in cognitively impaired patients, which might be explained by poor understanding of instructions not to move or a lower baseline cerebral blood flow causing a lower signal to noise ratio in these individuals. The even lower availability of all signals (37.2%) during repeated sit to stand transitions in this pooled cohort can be attributed to the abundant occurrence of transition induced movement artefacts. Due to removal of negative phase shifts, the number of individuals for whom both NIRS- and TCD-derived CA measures were available was further reduced, posing a substantial limitation to the applicability of NIRS-based CA estimation. Further efforts should be made to decrease NIRS sensitivity to movement artefacts to enhance its applicability for CA estimation.

TCD is the gold standard for CA assessment, but also has limitations. TCD-derived CA measures have limited reproducibility,[20,22,29] potentially indicating that physiological factors apart from CA may influence cerebral blood flow velocity and hence TCD-derived CA measures. These factors may also partly explain the poor correlation with NIRS-derived CA estimates. TCD signals had to be discarded due to artefacts in some individuals with good quality BP and NIRS signals, limiting the number of individuals that could be included in the comparative analyses.

Strength and limitations

The strength of this study is the diversity of the included cohorts and the simultaneous measurements of BP, TCD and NIRS both during well standardized (supine rest) and CA challenging (repeated sit to stand transitions) test conditions. Limitations include the relatively short duration of the measurements, the differences between the NIRS devices used in the different cohorts and the relatively large proportion of data that could not be used in the final analysis due to the presence of artefacts.

Conclusion and clinical implications

Criterion validity of NIRS-derived CA estimates increases after correction for non-CA effects arising from the cerebral microvasculature and may be sufficient to enable comparisons between groups, though insufficient for clinical application in individuals. The results suggest that NIRS-derived CA estimates may be particularly valid during repeated sit to stand transitions. However, artefacts in NIRS recordings impede CA estimation as indicated by the substantial proportion of the data that had to be discarded. Reducing motion artefacts is needed to increase quality of measurements during transitions and the applicability of NIRS-derived CA estimation. Increasing the quality of NIRS-derived CA estimation during supine rest could be performed by

prolonging measurements and selecting data segments with more BP variation. After optimization of measurement duration, NIRS device settings, measurement protocol and artefact removal, NIRS measurements in geriatric outpatients may potentially enable valid CA assessment in a wider range of patients during more instances.

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Supplementary file S11.1

Cerebral autoregulation (CA) may be estimated using the blood pressure (BP) to oxygenated hemoglobin (O_2Hb) transfer function phase shift (TF_φ). However, as O_2Hb not only reflects cerebral blood flow, but is also affected by the cerebral microcirculation, the BP-O_2Hb TF_φ should be corrected for cerebral microcirculation effects to approximate the BP to cerebral blood flow velocity (CBFV) TF_φ used as a gold standard measure of CA.

Effects from the cerebral microcirculation are reflected by the CBFV-O_2Hb $TF_{\varphi,}$ which can be subtracted from the BP-O_2Hb TF_φ (figure S11.1.1) As CBFV and O_2Hb are similarly influenced by cerebral autoregulation, this subtraction does not result in a loss of cerebral autoregulation information reflected by the BP-O_2Hb TF_φ. However, computation of CBFV-O_2Hb TF_φ requires transcranial Doppler (TCD) measurements, a requirement which was aimed to be eliminated. The CBFV-O_2Hb TF_φ should therefore be estimated without the use of TCD measurements. As demonstated in Figure S11.1.1, the CBFV-O_2Hb TF_φ can be estimated using the mean of the BP-O_2Hb TF_φ in the high frequency range (HF, 0.2 – 0.5 Hz), which is typically negative. Correcting the BP-O_2Hb TF_φ for cerebral microcirculation effects can hence be performed by subtracting its mean in the HF range.

To test the hypothesis that cerebral microcirculation effects reflected by the CBFV-O_2Hb TF_φ particularly comprise waveform steepness decline between macro- and microcirculation, signals with different waveform steepness were simulated and their TF_φ was computed (Figure S11.1.2). The CBFV and O_2Hb signals were simulated using 3000 heart beats with a random period between 0.8 and 1.2 seconds and superposed white noise. Heart beats in the CBFV and O_2Hb signal were simulated using triangles with a peaks at 5% and 45% of the heart cycle, respectively.

The phase shift of the transfer function between these two simulated signals with different waveform steepness (Figure S11.1.2) resembled the CBFV-O_2Hb TF_φ in Figure S11.1.1 (fairly constant negative phase shift in LF and HF ranges). This finding indicates that waveform steepness decline in the cerebral microcirculation is an important effect to be corrected for when estimating CA using the BP-O_2Hb TF_φ.

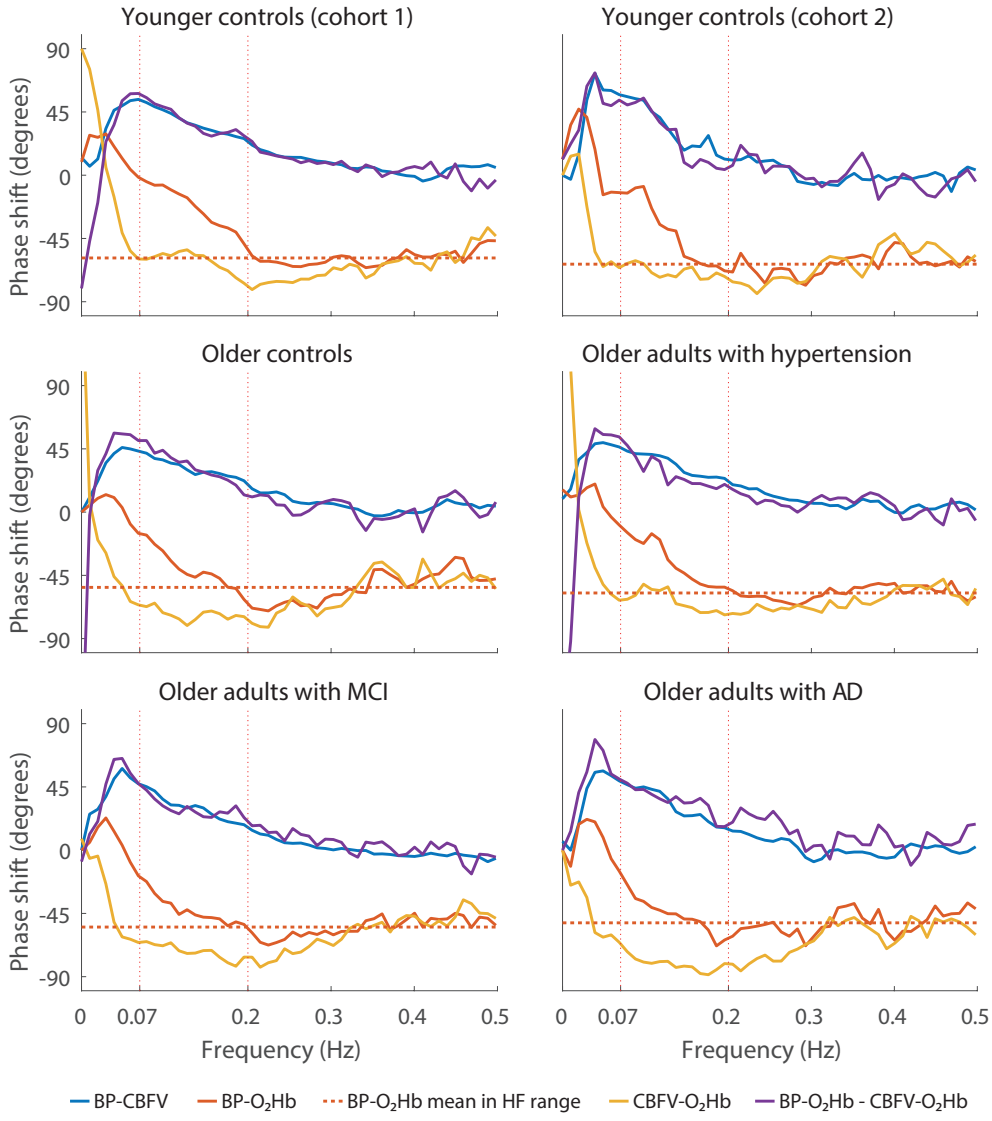

Figure S11.1.1. Grand average of BP-CBFV, BP-O2Hb and CBFV-O2Hb TFφ in supine rest, per cohort. The red dotted lines are the means lines of the BP-O2Hb TFφ in the high frequency (HF) range. MCI: mild cognitive impairment; AD: Alzheimer's dementia.

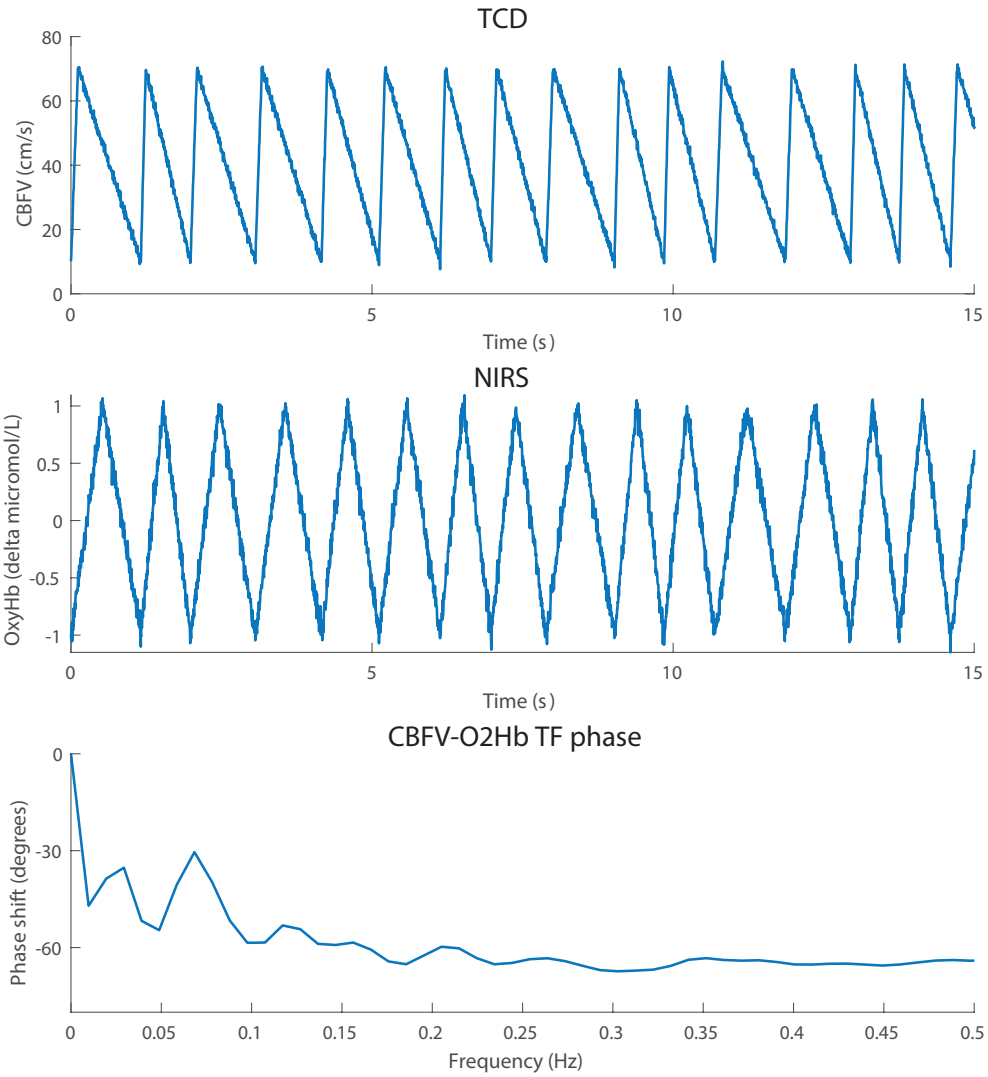

Figure S11.1.2. Simulated CBFV and O2Hb signals and their transfer function phase shift. The first 15 seconds are displayed. The entire signal comprised 3000 heart beats.

Supplementary Table S11.2: Transfer function analysis results during supine rest and repeated sit-to-stand transitions

	Supine rest										Sit to stand transitions	
	Younger controls (N=53)		Older controls (N=28)		Hyper-tension patients (N=27)		Cognitively impaired patients (N=94)		All (N=202)		Cognitively impaired patients (N = 94)	
BP-CBFV												
VLF												
Gain, cm/s/mmHg, mean (SD)	52	0.55 (0.22)	23	0.53 (0.14)	25	0.45 (0.19)	70	0.44 (0.15)	170	0.49 (0.18)	71	0.45 (0.24)
Phase, degrees, mean (SD)	52	50 (27)	23	42 (14)	25	48 (23)	70	52 (29)	170	50 (26)	71	47 (13)
Coherence [0-1], mean (SD)	53	0.43 (0.18)	23	0.54 (0.16)	26	0.48 (0.21)	72	0.53 (0.16)	174	0.49 (0.18)	71	0.81 (0.15)
LF												
Gain, cm/s/mmHg, mean (SD)	53	0.91 (0.33)	23	0.78 (0.23)	26	0.63 (0.27)	72	0.65 (0.20)	174	0.74 (0.28)	70	0.53 (0.27)
Phase, degrees, mean (SD)	53	37 (16)	23	30 (9)	26	34 (10)	72	31 (18)	174	33 (16)	70	24 (13)
Coherence [0-1], mean (SD)	53	0.69 (0.17)	23	0.69 (0.21)	26	0.63 (0.22)	72	0.63 (0.21)	174	0.66 (0.20)	71	0.67 (0.18)
HF												
Gain, cm/s/mmHg, mean (SD)	53	1.04 (0.35)	23	0.87 (0.26)	26	0.67 (0.28)	71	0.70 (0.28)	173	0.82 (0.33)	70	0.43 (0.23)
Phase, degrees, mean (SD)	53	6 (15)	23	5 (8)	26	8 (11)	71	1 (19)	173	4 (16)	70	0 (14)
Coherence [0-1], mean (SD)	53	0.64 (0.20)	23	0.67 (0.22)	26	0.56 (0.27)	72	0.63 (0.24)	174	0.63 (0.23)	71	0.68 (0.21)
BP-O_2Hb												
VLF												
Gain, cm/s/mmHg, mean (SD)	44	0.06 (0.03)	20	0.10 (0.05)	19	0.04 (0.01)	67	0.05 (0.02)	150	0.06 (0.03)	40	0.05 (0.03)
Phase, degrees, mean (SD)	41	72 (33)	19	59 (19)	18	60 (21)	61	60 (25)	139	63 (27)	38	44 (20)
Coherence [0-1], mean (SD)	47	0.39 (0.17)	21	0.50 (0.23)	23	0.40 (0.22)	73	0.45 (0.18)	164	0.43 (0.19)	42	0.71 (0.21)
LF												
Gain, cm/s/mmHg, mean (SD)	46	0.06 (0.03)	20	0.08 (0.04)	23	0.04 (0.02)	71	0.04 (0.02)	160	0.05 (0.03)	41	0.04 (0.02)
Phase, degrees, mean (SD)	41	33 (31)	19	17 (15)	21	20 (27)	64	12 (25)	145	20 (27)	39	9 (26)
Coherence [0-1], mean (SD)	47	0.51 (0.22)	21	0.46 (0.23)	23	0.52 (0.26)	73	0.44 (0.22)	164	0.48 (0.23)	42	0.44 (0.14)
HF												
Gain, cm/s/mmHg, mean (SD)	46	0.04 (0.02)	21	0.05 (0.02)	22	0.03 (0.01)	73	0.02 (0.01)	162	0.03 (0.02)	42	0.02 (0.01)
Phase, degrees, mean (SD)	41	-0 (34)	20	2 (33)	21	-0 (28)	65	0 (31)	147	0 (32)	39	-3 (61)
Coherence [0-1], mean (SD)	47	0.43 (0.23)	21	0.29 (0.19)	23	0.45 (0.29)	73	0.35 (0.20)	164	0.38 (0.23)	42	0.34 (0.16)

Results of BP-CBFV and BP-O_2Hb transfer function analysis, expressed as mean gain, phase and coherence in the very low frequency (VLF), low frequency (LF) and high frequency (HF) range, per group. SD: standard deviation.

Chapter 12

General discussion and conclusions

General discussion

This thesis investigated the diagnostics of orthostatic hypotension (OH), which according to the consensus definition is a sustained systolic/diastolic blood pressure (BP) drop larger than 20/10 mmHg within 3 minutes after standing up. Current OH diagnostics is limited due to 1) contradictory evidence on the association between the consensus OH definition and physical functioning and falls; 2) the uncertainty of the clinical value of continuous BP measurements, which may in contrast to intermittent sphygmomanometer measurements reflect the challenge posed to compensation systems and brain exposure to low perfusion pressures; and 3) the lack of assessment of systems compensating for orthostatic BP drops such as baroreflex sensitivity (i.e., heart rate increase in response to a BP drop to stabilize BP), peripheral vasoconstriction (i.e., narrowing of peripheral artery diameter in response to a BP drop to increase peripheral resistance and stabilize BP) and cerebral autoregulation (i.e., dilation of cerebral arterioles in response to a BP drop to keep cerebral blood flow constant).

This thesis aimed 1) to further determine the clinical value of the currently used consensus OH definition by pooling the existing evidence regarding the association between OH and physical functioning and falls; 2) to assess the clinical value of assessing BP drop rate and BP recovery derived from continuous BP measurements, which may reflect the challenge posed to compensation systems and brain exposure to low perfusion pressures, respectively; 3) to explore the potential added value of assessing systems compensating for orthostatic BP drops. To measure these compensation systems, photoplethysmography (PPG), electrocardiography (ECG) and near-infrared spectroscopy (NIRS) were used, which were selected because they are suitable to be further developed for ambulatory use.

The first aim was addressed using meta-analyses including 63 studies and 51,000 individuals (**chapters 2-3**). OH was found to be associated with balance performance, activities of daily living and falls in older adults, but not with mobility (i.e., self-reported mobility problems or the use of walking aids), walking speed and subjectively reported physical activity.

The second aim was addressed by determining the association of BP drop rate and recovery with physical and cognitive performance, frailty and falls in geriatric outpatients. BP drop rate derived from continuous BP measurements was shown to be associated with physical performance, frailty and falls in a cohort of 168 geriatric outpatients (**chapters 4-5**). BP recovery derived from continuous BP measurements, particularly diastolic blood pressure recovery in the interval between 30 and 60 seconds after standing up, was associated with physical performance, frailty and falls in geriatric outpatients, but not with cognitive performance (**chapter 6**).

The third aim was addressed by assessing the sensitivity (i.e., the capacity to record physiological changes in response to postural change), test-retest reliability

(i.e., the property to measure similar values during similar postural changes) and validity (i.e., the extent to which the parameter reflects the underlying physiology) of parameters expressing baroreflex sensitivity, peripheral vasoconstriction, cerebral oxygenation and autoregulation derived from combined PPG, ECG and NIRS measurements. Cerebral oxygenation changes measured with NIRS during standing up were shown to be sensitive and reliable during different types and speeds of postural changes and to discriminate between standing up from sitting and standing position in 15 young adults (**chapter 7**). Cerebral autoregulation parameters derived from PPG, ECG and NIRS measurements were shown to be reliable and valid: PPG-NIRS-derived cerebral autoregulation parameters in the time domain correlated with BP-NIRS-derived cerebral autoregulation parameters in 34 young adults. PPG-derived baroreflex sensitivity had a poor to fair test-retest reliability and validity assessed by its correlation with BP-derived baroreflex sensitivity in this population (**chapter 8**). Pulse transit time derived from PPG-ECG measurements was sensitive to vasoconstriction provocation and postural change, but its validity as reflected by its correlation with total peripheral resistance could not be demonstrated (**chapter 9**). Baroreflex sensitivity was lower in older adults compared to young adults. The magnitude of cerebral oxygenation drop after standing up was smaller in older adults compared to young adults, but its recovery lasted longer (**chapter 10**)**.** Cerebral autoregulation parameters derived from NIRS in the frequency domain were shown to be valid compared to Transcranial Doppler (TCD) as a gold standard in younger and older adults, patients with controlled hypertension and cognitively impaired patients (**chapter 11**)**.**

The clinical value of the consensus orthostatic hypotension definition

The found associations between OH and balance performance, activities of daily living and falls (chapter 2-3) indicate the clinical value of the consensus OH definition, though a causal pathway cannot be inferred from the results, and the association could not be adjusted for potential confounders such as age. A causal pathway leading from OH to impaired physical functioning and falls is plausible, as a previous study reported OH to be associated with microvascular brain damage, which might impair physical functioning and increase fall risk.[1] Furthermore, a separate meta-analysis only including longitudinal studies also showed a strong association between OH and falls.

The effect size of the association between OH and falls was particularly high when OH was assessed using continuous BP measurements, suggesting continuous BP measurements to be preferable over intermittent sphygmomanometer BP measurements, which are most often used to diagnose OH.

The absence of an association between OH and physical functioning measures as physical activity and mobility may indicate that OH does not lead to decreased physical activity and impaired mobility. Alternatively, explanations could be sought

in the heterogeneity of the physical activity and mobility measures due to different assessment methods across the included studies.

The results suggest that orthostatic BP should be assessed in older adults, preferably using continuous BP measurements. Further studies on the association between OH and clinical outcome should preferably have a longitudinal design and use objective outcomes (e.g., using accelerometers) to maximize comparability between studies.

Orthostatic BP drop rate and BP recovery: the OH definition revisited

Orthostatic BP drop rate and BP recovery may reflect the challenge posed to compensation systems and brain exposure to low perfusion pressures, respectively, and were assessed using continuous orthostatic BP measurements.

The finding that BP drop rate derived from continuous orthostatic BP measurements was found to be more strongly associated with clinical outcome compared to orthostatic BP drop magnitude (chapter 4 and 5) suggests that the baroreflex and cerebral autoregulation may be challenged beyond their capacity by large BP drop rates rather than by large BP drop magnitudes. BP drop rate may in the context of an intrinsic baroreflex and cerebral autoregulation time delay[2–4] cause a temporary decreased cardiac output and cerebral perfusion and thereby have a negative impact on clinical outcome. However, the role of the baroreflex and cerebral autoregulation as intermediates in any causal pathway between BP drop rate and clinical outcome was not demonstrated in this thesis. An alternative explanation may be that both a large BP drop rate and poor clinical outcome measures are a reflection of a poorly functioning autonomous nervous system. However, adjusting for baroreflex sensitivity as an indicator of autonomous nervous system function did not change the strength of the found association (chapter 5).

The found association between BP recovery derived from continuous orthostatic BP measurements and clinical outcome (chapter 6) might indicate that BP recovery parameters express cerebral exposure to low perfusion pressures. However, cerebral perfusion pressures were not measured and cerebral autoregulation would compensate for this under physiological circumstances.[5] The results indicate diastolic BP recovery between 30-60 seconds after standing up as the potentially most clinically relevant parameter. This suggests that the brain might be particularly sensitive to hypoperfusion in this episode, but explanations remain hypothetical.

Overall, the results from chapter 4-6 indicate that parameters derived from continuous BP measurements during standing up have clinical value. These results suggest that continuous BP measurements are to be preferred over intermittent BP measurements as BP drop rate and recovery cannot be derived from intermittent BP measurements.

Continuous orthostatic BP measurements are often not available and good quality measurements are not feasible in approximately 20% of geriatric outpatients

due to high arterial stiffness,[6] highlighting the need to invest in low cost, minimally obtrusive alternative techniques to assess continuous orthostatic BP.

The results support the use of an enhanced OH definition, incorporating BP drop rate and BP recovery. Such a definition might for example define OH as a systolic BP drop rate larger than 3.1 mmHg/s (the median in the investigated cohort in chapter 5) and/or no diastolic recovery above baseline in 30-60 seconds after standing up (this parameter was found to have the highest clinical value in chapter 6). The optimal cutoffs in this enhanced OH definition should be further established in independent studies and cohorts, assessing sensitivity and specificity of for clinical outcome (e.g. orthostatic intolerance and falls) as a function of the used cutoffs.

Other topics to be addressed are whether BP drop rate and BP recovery derived from continuous orthostatic BP measurements are predictive for clinical outcome decline and whether treatment based on these parameters (e.g., starting midodrine, i.e., antihypotensive medication, if orthostatic systolic BP drop rate > 3.1 mmHg/s) improves clinical outcome. These topics require longitudinal study designs.

Baroreflex sensitivity, peripheral vasoconstriction, cerebral oxygenation and autoregulation: parameters potentially advancing OH diagnostics

Parameters expressing baroreflex sensitivity

Baroreflex sensitivity parameters based on PPG and BP were defined as the orthostatic change in heart rate divided by change in estimated or measured BP, respectively. Estimated BP was based on the finger PPG signal.

PPG-based baroreflex sensitivity during standing up had a poor to fair test-retest reliability in younger adults (chapter 8), potentially indicating that motion artifacts in the PPG signals may have had a negative influence. Alternatively, factors not related to standing up such as emotion, mood and respiration may have had a negative influence. The validity of PPG-based baroreflex sensitivity assessed by its correlation with BP-based baroreflex sensitivity in younger adults (chapter 8) was highest if assessed during rapid standing up from supine position. Overall, the results support further investigation of the clinical value of PPG-based baroreflex sensitivity, provided that measurements are performed during rapid standing up from supine position, which requires a controlled environment. The results suggest that reliable PPG-based baroreflex sensitivity estimates are not yet feasible in the home setting as standing up in the home situation is difficult to standardize. As PPG-based baroreflex sensitivity estimates still have the unpractical requirement of calibration using continuous BP measurements, further research should focus on the question whether this calibration can also be performed using the more widely available sphygmomanometer BP measurements. This would require simultaneous PPG and sphygmomanometer BP measurements during stable BPs at different values. For example, two test conditions might be used for calibration: supine rest

and a sustained hand grip exercise. BP in supine rest is usually stable and relatively low, as demonstrated in this thesis, enabling the reliable simultaneous reading of sphygmomanometer BP and PPG. A sustained hand grip exercise increases BP to a new stable value. The BP and PPG values from the two conditions may be used to calibrate the PPG measurement.

BP-based baroreflex sensitivity was found have an excellent and good test-retest reliability in younger and older adults, respectively, only when assessed during standing up from supine position (chapter 10). The finding that BP-based baroreflex sensitivity was significantly lower in older adults compared to younger adults, irrespective of the type of postural change (chapter 10), is an indication for its validity, and suggests that older adults are more vulnerable for OH. The results support assessment of the clinical value of this parameter in further studies and suggest that these assessments should be performed during standing up from supine position.

Pulse transit time as a proxy for peripheral vasoconstriction

Pulse transit time (PTT), defined as the time between the R-peak in the ECG and the peak in the first derivative in wrist or finger PPG, was investigated as a parameter potentially expressing peripheral vasoconstriction.[7]

The computation of PTT requires high quality PPG signals. Wrist and finger PPG signals did not pass data quality assessment in 23% and 42% of the older adults, respectively (chapter 9), indicating that efforts to improve PPG signal acquisition are necessary.

The test-retest reliability results were in favor of the use of finger PPG rather than wrist PPG to compute PTT (chapter 9). In the participants with good quality finger PPG signals, finger PTT sensitivity to both vasoconstriction provocation by the cold pressor test and active standing up was demonstrated, in both younger and older adults, indicating that finger PTT may reflect vasoconstriction. The validity of finger PTT as a proxy for vasoconstriction as assessed by its correlation with total peripheral resistance could not be demonstrated, neither were PTT responses after standing up significantly different between younger and older adults (chapter 9). Overall, the results suggest that PTT cannot be used as a reliable proxy for vasoconstriction. As PTT was found to be associated with BP (chapter 8 and 9) and supine resting PTT before standing up was associated with BP drop after standing up (chapter 9), further studies may rather focus on the role of finger PTT to estimate or predict BP.

Parameters expressing cerebral oxygenation

The main investigated cerebral oxygenation parameters were oxygenated and deoxygenated hemoglobin (O_2Hb and HHb) drop magnitude, defined as their lowest value within 30 seconds after standing up minus baseline, and O_2Hb initial recovery

time, defined as the time from start of standing up until the first peak after the aforementioned drop.

O_2Hb and HHb measured using NIRS during standing up from supine position were of good quality in 30/34 (88.2%) younger adults and in 28/31 (90.3%) older adults (chapter 10), indicating their potential use in clinical practice.

O_2Hb drop magnitude was demonstrated to be particularly sensitive to postural change in younger and older adults (chapter 7, 8 and 10), differentiating between standing up from supine and sitting position in younger adults, but not between slow and rapid standing up (chapter 7); and to have an excellent test-retest reliability during standing up from supine position in both younger and older adults (chapter 10). Results on the validity of O_2Hb response after standing up assessed by its association with age were ambiguous as the O_2Hb drop magnitude was negatively associated with age (chapter 10), which is not in line with the expected smaller attenuation of cerebral oxygenation fluctuations by cerebral autoregulation in older adults compared to young adults. This finding may be explained by a lower baseline cerebral blood flow and cerebral oxygen level in older adults compared to young adults[8,9] or by assumptions on the distance travelled by light in the brain, as discussed in chapter 10. On the other hand, O_2Hb initial recovery time lasted longer in older adults, suggesting the validity of this parameter.

The findings support further study on O_2Hb drop magnitude and O_2Hb initial recovery time derived from NIRS as parameters expressing cerebral oxygenation. Further research should address the clinical value O_2Hb drop magnitude and O_2Hb initial recovery time assessed during standing up in geriatric outpatients, for example by their predictive value for orthostatic intolerance and falls. If these parameters can be demonstrated to have clinical value, they may have to be incorporated in the future OH definition.

Further development should improve the robustness of the NIRS measurement to further increase the proportion of good quality signals, which might be performed by adapting and personalizing sensor attachment to the patient. Further development should also aim to optimize the NIRS measurement for application in the home setting by replacing wires with wireless modules and improving patient-friendliness.

Parameters expressing cerebral autoregulation

Cerebral autoregulation parameters in both time and frequency domain were assessed. Time domain cerebral autoregulation parameters were defined as orthostatic O_2Hb drop magnitude divided by measured or estimated BP drop (ΔO_2Hb/ΔBP); the investigated frequency domain parameter as the phase shift of the BP to O_2Hb transfer function (TF).

ΔO_2Hb/ΔBP had a fair test-retest reliability and an excellent validity only during rapid standing up from supine position in younger adults (chapter 8), indicating that assessment of the clinical value of this parameter is worthwhile provided that

measurements are performed in a controlled environment to standardize the rapid supine to stand transitions. As for baroreflex sensitivity, the currently necessary calibration using continuous BP measurements should be circumvented for this parameter to be useful in clinical practice. Alternative calibration methods as suggested above should therefore be investigated.

The validity of cerebral autoregulation parameters computed in the frequency domain was demonstrated using cerebral blood flow velocity measured using Transcranial Doppler (TCD) as a gold standard. The results indicated the validity of NIRS-based cerebral autoregulation estimation as the BP to O_2Hb TF phase shift correlated with measures of cerebral autoregulation derived from TCD in a group consisting of younger and older adults, patients with controlled hypertension and patients with cognitive impairment (chapter 11).

Overall, both time and frequency domain parameters of cerebral autoregulation may be valuable in clinical practice, though the validity of the frequency domain parameters has been further validated in clinical populations compared to the investigated time domain parameter. For both types of parameters, the clinical value needs to be addressed.

Parameters most likely to contribute to OH diagnostics

The parameters for which an indication of validity was shown in older adults or geriatric outpatients were 1) baroreflex sensitivity (association with age, chapter 10), 2) cerebral oxygenation expressed by O_2Hb drop magnitude and recovery time (association with age, chapter 10), and 3) cerebral autoregulation expressed by frequency domain parameters (correlation with TCD-derived cerebral autoregulation, chapter 11). Baroreflex sensitivity and frequency domain parameters of cerebral autoregulation assessed under standardized conditions may particularly advance OH diagnostics by quantifying the compensatory capacity for orthostatic BP drops in a clinical setting. O_2Hb drop magnitude and recovery time are more likely to contribute to OH diagnostics by reflecting cerebral autoregulation efficacy during daily life conditions in the home situation.

General conclusions and future directions

In conclusion, the OH consensus definition was found to be clinically valuable as patients diagnosed according to this definition are at increased risk of impaired physical functioning and falls. However, this definition is likely to miss clinically relevant information on the intensity of the challenge posed to compensation systems and cerebral exposure to low perfusion pressures as it does not account for the BP course within one minute after standing up. This information may be reflected by orthostatic BP drop rate and BP recovery derived from continuous BP measurements, which were found to have added clinical value by their association with clinical outcome. BP drop rate and BP recovery may after confirmation of the

results in further studies have to be incorporated in a new OH definition for continuous orthostatic BP measurements to better identify individuals with clinical consequences due to OH. To further advance OH diagnostics, assessment of baroreflex sensitivity, cerebral oxygenation and cerebral autoregulation should be included. Parameters expressing these physiological quantities were by their sensitivity, test-retest reliability and validity in younger and older adults demonstrated to be potentially valuable, supporting further study on the clinical value of these parameters.

Further longitudinal studies should assess the predictive value of BP drop rate, BP recovery, baroreflex sensitivity, cerebral oxygenation and autoregulation for clinical outcome, e.g. physical and cognitive performance, frailty, falls and mortality. As continuous BP measurements are essential for the computation of BP drop rate, BP recovery, baroreflex sensitivity and cerebral autoregulation, there is a need for low cost and minimally obtrusive BP estimation, which has to be addressed in further studies.

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Summary

English summary

Nederlandse samenvatting

Summary

This thesis investigated the diagnostics of orthostatic hypotension (OH). OH is defined as a sustained systolic/diastolic blood pressure (BP) drop larger than 20/10 mmHg within 3 minutes after standing up. OH is common among older adults aged above 65 years (6 – 31%) and geriatric outpatients (22-56%), sometimes accompanied by orthostatic intolerance (dizziness, light-headedness and blurry vision) and associated with poor clinical outcome (cardiovascular diseases, impaired cognitive performance and mortality). Current OH diagnostics is limited due to 1) contradictory evidence on the association between the OH definition and physical functioning and falls; 2) the uncertainty of the clinical value of continuous BP measurements, which may in contrast to intermittent sphygmomanometer measurements reflect the challenge posed to compensation systems and brain exposure to low perfusion pressures; and 3) the lack of assessment of systems compensating for orthostatic BP drops such as baroreflex sensitivity (i.e., heart rate increase in response to a BP drop to stabilize BP), peripheral vasoconstriction (i.e., narrowing of peripheral artery diameter in response to a BP drop to increase peripheral resistance and stabilize BP) and cerebral autoregulation (i.e., dilation of cerebral arterioles in response to a BP drop to keep cerebral blood flow constant).

This thesis aimed 1) to further determine the clinical value of the currently used OH definition by pooling the existing evidence regarding the association between OH and physical functioning and falls; 2) to assess the clinical value of assessing BP drop rate and BP recovery derived from continuous BP measurements, which may reflect the challenge posed to compensation systems and brain exposure to low perfusion pressures, respectively; 3) to explore the potential added value of assessing systems compensating for orthostatic BP drops. To measure these compensation systems, photoplethysmography (PPG), electrocardiography (ECG) and near-infrared spectroscopy (NIRS) were used. PPG measures changes in artery diameter due to BP pulse waves, ECG measures the electrical activity of the heart and NIRS measures changes in cerebral oxygen concentration.

The first aim was addressed using meta-analyses including 63 studies and 51,000 individuals. OH was found to be associated with balance performance, activities of daily living and falls in older adults, but not with mobility (i.e., self-reported mobility problems or the use of walking aids), walking speed and subjectively reported physical activity. These results demonstrate the value of the currently used OH definition in clinical practice as well as the need for research on OH diagnostics and therapeutics. However, the currently used OH definition is likely to miss clinically relevant information on the intensity of the challenge posed to compensation systems and cerebral exposure to low perfusion pressures as it does not account for the BP course within one minute after standing up.

The second aim was to overcome this shortcoming by assessing BP drop rate

and recovery derived from continuous BP measurements, which enable measurement of the orthostatic BP within one minute after standing up. BP drop rate and recovery were found to be valuable as they were associated with physical performance, frailty and falls in geriatric outpatients. The results advocate the use of continuous BP monitors in clinical practice, though their availability is currently limited. The results demonstrate the importance of assessing BP drop rate and recovery and suggest their incorporation in an enhanced OH definition after confirmation of the findings in further studies.

The third aim was addressed by assessing the sensitivity (i.e., the capacity to record physiological changes in response to postural change), test-retest reliability (i.e., the property to measure similar values during similar postural changes) and validity (i.e., the extent to which the parameter reflects the underlying physiology) of parameters expressing baroreflex sensitivity, peripheral vasoconstriction, cerebral oxygenation and autoregulation. Sensitivity for postural changes could be demonstrated for all of the investigated parameters. Test-retest reliability could for most parameters only be demonstrated during specific standardized postural changes, i.e., during standing up from supine position. Validity in older adults or geriatric outpatients was only shown for parameters expressing baroreflex sensitivity, orthostatic cerebral oxygenation drop and cerebral autoregulation. The results are prerequisites for clinical use of these parameters, but their predictive value for e.g. physical and cognitive performance, frailty, falls and mortality needs to be assessed in further longitudinal studies.

In conclusion, the currently used OH definition was found to be clinically valuable as patients diagnosed according to this definition are at increased risk of impaired physical functioning and falls. BP drop rate and BP recovery derived from continuous BP measurements were found to have added clinical value by their association with clinical outcome and may after confirmation of the results in further studies have to be incorporated in a new OH definition for continuous orthostatic BP measurements to better identify individuals with clinical consequences due to OH. Parameters expressing baroreflex sensitivity, cerebral oxygenation and cerebral autoregulation were by their sensitivity, test-retest reliability and validity in younger and older adults demonstrated to be potentially valuable, supporting further study on the clinical value of these parameters.

Nederlandse samenvatting

In dit proefschrift werd de diagnostiek van orthostatische hypotensie (OH) onderzocht. OH is gedefinieerd als een daling van de systolische/diastolische bloeddruk van meer dan 20/10 mmHg ten opzichte van de liggende situatie binnen drie minuten na het opstaan die niet volledig herstelt. OH komt veel voor onder ouderen met een leeftijd boven de 65 jaar (6 - 31%) en geriatrische patiënten (22 - 56%), gaat soms gepaard met symptomen van duizeligheid, een licht gevoel in het hoofd en wazig zien en is geassocieerd met een slechte klinische uitkomst (hart- en vaatziekten, verminderd cognitief presteren en mortaliteit). De huidige OH-diagnostiek is beperkt door 1) conflicterend bewijs over de associatie tussen OH en fysiek functioneren en vallen; 2) de onduidelijkheid over de klinische waarde van continue bloeddrukmetingen, die in tegenstelling tot de klassieke sfygmomanometer metingen de mate waarin compensatiesystemen worden uitgedaagd door een houdingsverandering en de blootstelling van de hersenen aan lage perfusiedrukken kunnen weergeven; 3) het ontbreken van beoordeling van systemen die compenseren voor bloeddrukdaling na het opstaan, zoals de baroreflex (het stijgen van de hartfrequentie als reactie op een bloeddrukdaling met als doel de bloeddruk te stabiliseren), perifere vasoconstrictie (het vernauwen van de perifere slagaders om de perifere weerstand omhoog te brengen en de bloeddruk te stabiliseren) en cerebrale autoregulatie (het verwijden van slagaders in de hersenen als reactie op een bloeddrukdaling om de bloedstroom naar de hersenen constant te houden).

In dit proefschrift werd beoogd 1) de klinische waarde van de in de praktijk gebruikte OH-definitie verder te bepalen door het bestaande bewijs over de associatie tussen OH en fysiek functioneren en vallen gezamenlijk te analyseren; 2) de klinische waarde vast te stellen van het bepalen van de snelheid van de bloeddrukdaling en de grootte van het bloeddrukherstel na het opstaan middels continue bloeddrukmetingen; 3) te bepalen of het meten van systemen die compenseren voor bloeddrukdaling na het opstaan zinvol kan zijn om de OH-diagnostiek te verbeteren. Om deze compensatiesystemen te meten, werd gebruik gemaakt van fotoplethysmografie (PPG), elektrocardiografie (ECG) en near-infrared spectroscopy (NIRS) metingen. PPG meet de diameterverandering van een slagader als reactie op voorbijkomende bloeddrukgolven, ECG meet de elektrische activiteit van het hart en NIRS meet zuurstofconcentratieverandering in de hersenen.

Voor het eerste doel van dit proefschrift werd een meta-analyse uitgevoerd van 63 studies en 51,000 individuen. Hieruit bleek dat OH was geassocieerd met verminderde prestaties op balanstests, het minder kunnen uitvoeren van activiteiten van het dagelijks leven, en vallen, maar niet met mobiliteit (zelf-gerapporteerde mobiliteitsproblemen of het gebruik van een hulpmiddel bij het lopen), loopsnelheid en fysieke activiteit. De resultaten suggereren dat verder onderzoek naar OH-diagnostiek en behandeling zinvol is om mogelijk achteruitgang van fysiek

functioneren en vallen te voorkomen. Gebruik van de OH-definitie in de klinische praktijk helpt mogelijk bij het identificeren van patiënten met verhoogd valrisico. Echter, de OH-definitie mist waarschijnlijk klinisch relevante informatie over de mate waarin compensatiesystemen worden uitgedaagd door een houdingsverandering en de blootstelling van de hersenen aan lage perfusiedrukken doordat deze geen rekening houdt met het bloeddrukverloop binnen één minuut na het opstaan.

Het tweede doel van dit proefschrift was om deze tekortkoming te verbeteren door het bepalen van de snelheid van de bloeddrukdaling en de grootte van het bloeddrukherstel na het opstaan. Deze parameters kunnen worden bepaald middels continue bloeddrukmetingen, die het mogelijk maken om het bloeddrukverloop binnen één minuut na het opstaan te meten. De parameters werden waardevol bevonden in dit proefschrift omdat ze geassocieerd waren met fysieke prestaties, kwetsbaarheid en vallen onder patiënten op de geriatrische polikliniek. De resultaten laten zien dat het zinvol is om continue bloeddrukmetingen tijdens het opstaan uit te voeren op de geriatrische polikliniek, hoewel de beschikbaarheid van continue bloeddrukmeters nog beperkt is. De resultaten laten specifiek zien dat bepaling van de snelheid van de bloeddrukdaling en de grootte van het bloeddrukherstel belangrijk is. Als de resultaten kunnen worden gerepliceerd is dit aanleiding om de definitie van OH te verbeteren door de genoemde parameters erin op te nemen.

Voor het derde doel van dit proefschrift werd de sensitiviteit, test-hertest betrouwbaarheid en validiteit van parameters die bovengenoemde compensatiesystemen moeten weergeven, bepaald. Sensitiviteit betekent dat de parameter reageert (verandert) na een houdingsverandering; test-hertest betrouwbaarheid dat deze verandering hetzelfde is als dezelfde houdingsverandering herhaald wordt; validiteit de mate waarin de parameter de onderliggende fysiologie weergeeft. Sensitiviteit kon worden aangetoond voor alle onderzochte parameters. Test-hertest betrouwbaarheid kon voor de meeste parameters alleen worden aangetoond voor een specifieke en gestandaardiseerde houdingsverandering, namelijk het opstaan vanuit liggende positie. In dit proefschrift werd validiteit in ouderen alleen aangetoond voor baroreflex sensitiviteit, cerebrale zuurstofdaling na het opstaan en cerebrale autoregulatie. Deze resultaten zijn een voorwaarde voor het klinisch gebruik van deze parameters, maar hun voorspellende waarde voor klinische uitkomsten (bijv. fysiek en cognitief functioneren, kwetsbaarheid, vallen en mortaliteit) moet nog bepaald worden in longitudinale studies.

Concluderend werd de in de praktijk gebruikte OH definitie van klinische waarde bevonden omdat volgens deze definitie gediagnostiseerde patiënten een verhoogd risico voor verminderd fysiek functioneren en vallen hadden. Parameters die de snelheid van de bloeddrukdaling en de grootte van het bloeddrukherstel na het opstaan uitdrukken en zijn afgeleid van continue bloeddrukmetingen werden van toegevoegde klinische waarde bevonden door hun associatie met klinische

uitkomsten. Deze parameters moeten na replicatie van de resultaten mogelijk worden opgenomen in een verbeterde OH definitie om individuen met negatieve klinische consequenties door OH beter te identificeren. Parameters die een weergave zijn van compensatiesystemen voor bloeddrukdaling werden potentieel waardevol bevonden door hun sensitiviteit, test-hertest betrouwbaarheid en validiteit, wat aantoont dat verder onderzoek naar de klinische waarde van deze parameters zinvol is.

Appendices

List of publications

Curriculum Vitae

Acknowledgments - Dankwoord

List of publications

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About the author

Arjen Mol was born on the January 25th 1991 in Ede, the Netherlands. He attended secondary school in Apeldoorn. There he developed a particular interest in medicine and technology, which he aimed to combine in his further career. He obtained his bachelor's degree in Technical Medicine (cum laude) at Twente University in Enschede in 2012 and his master's degree in Medicine (cum laude) at Utrecht University in 2016.

After his graduation he worked as a medical doctor at the Neurology department of the Radboud University Medical Center, Nijmegen, the Netherlands. In 2017, he started his PhD project on orthostatic hypotension diagnostics at the Vrije Universiteit Amsterdam, supervised by prof. Andrea Maier, prof. Richard van Wezel and dr. Carel Meskers. During his project he was awarded the Trainee Professional Development award, enabling him to visit the Society for Neuroscience annual meeting in Chicago in 2019, and was admitted to the Leadership Development Program, which apart from virtual conferences consisted of live meetings in Washington DC, USA. During his PhD project, Arjen presented his research for several national and international audiences.

Currently, Arjen is working as a medical doctor at the cardiology department of the Gelre hospital, Apeldoorn, the Netherlands.

Arjen is married and father of a son.

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